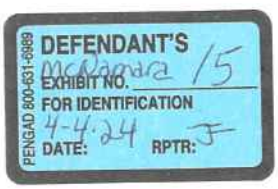
EXHIBIT 64

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

CASE NO: 2:22-cv-00184-LCB-CWB

BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; et al.,
Plaintiffs,
and
UNITED STATES OF AMERICA,
Plaintiff-Intervenor,
v.
STEVE MARSHALL, in his official Capacity as Attorney General of the State of Alabama, et al.,
Defendants.



DEPOSITION
OF
MORISSA J. LADINSKY, M.D.
APRIL 12, 2023

Deposition of MORISSA LADINSKY, M.D., called as a witness by the Defendants, before Jennifer Madaris, Certified Court Reporter for the State of Alabama, with principal offices in Jefferson County, commencing at 9:00 a.m., on the 12th day of April, 2023, at 20th Street North, Birmingham, Alabama 35203.

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I, Jennifer Madaris, CCR, RPR, a Court Reporter and Notary Public of the State of Alabama, acting as Commissioner, do certify that on this date, as provided by the Alabama Rules of Civil Procedure and the foregoing stipulation of counsel, there came before me at 20th Street North, Birmingham, Alabama 35203, on April 23 2023, beginning at 9:00 a.m., MORISSA LADINSKY, M.D., witness in the above cause for oral examination, whereupon the following proceedings were had:

MORISSA LADINSKY, M.D.

having been first duly sworn, was examined and testified as follows:

COURT REPORTER: Everyone on Zoom, please state your appearance.

MR. REINKE: Adam Reinke of King & Spalding on behalf of the private plaintiffs.

MR. SHORTNACY: Michael Shortnacy from King & Spalding also on behalf of the private plaintiffs.

MR. MINTER: Shannon Minter from NCLR also on behalf of the private plaintiffs.

MS. TOYAMA: My name is Kaitlin Toyama for the Department of Justice.

MR. BOWDRE: Bethany Lee and Bob Overing are from the Attorney General Office.

EXAMINATION BY MR. BROOKS:

Q. I am Roger Brooks with Alliance Defending Freedom representing Alabama, and I'll be asking a few questions today.

A. All right.

Q. Thank you for being here.

A. My pleasure.

MS. EAGAN: Before we get started we reserve the right to read and sign the deposition.

Q. (BY MR. BROOKS) And Dr. Ladinsky, let me ask first whether you have ever been through this deposition process before?

A. I've only been party to a deposition once, and that was in the context of a divorce, family law kind of thing ages ago.

Q. I'm not going to try to explain law to you, but you have seen the process?

A. Yes, sir, I have.

Q. I will ask questions. At any point feel free to ask for clarification if you think one of my questions is unclear. I'm going to show you a lot of documents today and ask you questions about documents. And I will hand you in advance to save trouble, there are four documents that I think we may refer to frequently enough that having them in one place as the pile builds up will be handy. And I'll tell you right now what those are. That includes a transcript of your testimony at the preliminary injunction hearing, your expert report submitted a couple of months ago in this matter, the Endocrine Society Guideline 2017 Edition, and a report -- a document that we, of course, will discuss that's titled the Cass Review.

A. Yes, sir.

Q. That's what's in this binder. Everything in it we will come to in due course, but I want you to have that in front of you.

A. Thank you.

MR. BROOKS: Let me ask the reporter to mark as Ladinsky Exhibit 1, a copy of the witness' curriculum vitae.

(Whereupon, Ladinsky Exhibit 1 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) And, Dr. Ladinsky, let me just ask: Does this appear to be a copy of your curriculum vitae?

A. It does.

Q. And am I correct that you consider yourself to be a pediatrician?

A. Correct.

Q. You have a license that is titled physician and surgeon, but am I correct that you are not a surgeon? That is simply the formal licensing title?

A. That is correct.

Q. All right. And you are not an endocrinologist; am I correct?

A. You are correct.

Q. And you're not a psychiatrist?

A. You are correct.

Q. And you have no degree in psychology?

A. I do not.

Q. Are you a neurologist?

A. I am not.

Q. And you consider yourself to be an expert in cognition and the study of development cognition?

A. On the level a primary care and board-certified pediatrician is and should be.

Q. That is, you have the expertise in cognition and developmental -- cognitive development that you consider to be standard for a pediatrician?

A. That's fair.

Q. But you don't consider yourself a specialist in cognition or cognitive development?

A. That's fair.

Q. Describe for me what training you have in adolescent developmental psychology.

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A. Again along the lines of a primary care pediatrician. We do a lot of work throughout residency, life experience, and a fellowship in academic general pediatrics. That takes that up to a level of being able to impart concepts to trainees, pediatric trainees. I also have 31 years of frontline work with the entire range of the pediatric population, 0 through about 21 or 22.

Q. Am I correct that you came to the University of Alabama Medical Center in 2015?

A. That's correct.

Q. And you came for the purpose of starting a pediatric gender clinic?

A. I would not say I came here to do that, no, sir.

Q. Okay.

A. No, sir. I came here to accept a faculty attending spot. This developed after I -- well, in proximate to.

Q. All right. Tell me -- describe for me if you would when you and colleagues decided to start that pediatric gender clinic.

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A. In 2014 in the lead-up to my relocation here or the early part of 2015. Because I relocated to Alabama in the summer of 2015 to take this position.

MS. EAGAN: I think he asked you when.

THE WITNESS: Okay.

Q. (BY MR. BROOKS) I asked you to describe when you and your colleagues formed the plan to start a pediatric gender clinic at the University of Alabama?

A. Sure. Absolutely. The early part of 2015.

Q. Okay. So essentially close in time to your move here?

A. That's fair.

Q. Okay. Is there any other gender clinic in the state of Alabama to your knowledge?

A. Not to my knowledge, no.

Q. And --

MS. EAGAN: Pediatric, correct?

MR. BROOKS: That is -- I will clarify the question.

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Q. Is there any other pediatric gender clinic in the state of Alabama?

A. There is not to my knowledge. I presume that's what you had been asking. I'm sorry.

MR. BROOKS: Thank you for the clarification.

Q. What number of pediatricians or primary care physicians in Alabama outside your clinic do you consider to be expert in diagnosing gender dysphoria?

MS. EAGAN: From her personal knowledge?

MR. BROOKS: Correct.

A. From my personal knowledge, I mean, primary care pediatricians are well trained and taught to recognize what could be emerging gender dysphoria. They don't -- no pediatrician has the level of expertise that, for example, a Ph.D. psychologist does --

Q. Well --

A. -- in that domain.

Q. -- how many pediatric physicians,

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primary care physicians in Alabama outside your clinic, in your view, have the expertise necessary to make an actual diagnosis of gender dysphoria in a child?

MS. EAGAN: Object to the form.

A. Tell me more about make a diagnosis. What do you mean in that way? Because do you mean it as it is asserted in guideline documents or as we may see that on the ground?

Q. (BY MR. BROOKS) Gender dysphoria is a mental health diagnosis defined in DSM-5; am I correct?

A. It is.

Q. And appropriately trained mental health professional may be tasked to make an evaluation as to whether a child does or does not fit the criteria for mental -- for gender dysphoria as set forth in DSM-5, correct?

A. Correct.

Q. That's what I mean by diagnosis. So my question is: How many primary care physicians in Alabama outside of your clinic, in your view, have the expertise necessary to actually make a

diagnosis of gender dysphoria according to the DSM-5 guidelines?

A. I could not answer that question.

Q. Your clinic receives referrals from doctors around the state; am I correct?

A. That's correct.

Q. Do you rely on doctors outside your clinic to make an actual diagnosis of gender dysphoria?

A. It's fair to say that we rely on doctors outside of our clinic to recognize gender dysphoria and recognize when referral to our clinic is necessary and warranted.

Q. Do you ever rely on doctors outside your clinic in Alabama to make a diagnosis of gender dysphoria as a sufficient basis to proceed with medical treatment or do you always insist on making a diagnosis within your own clinic?

A. I don't -- I mean, specifically -- restate that because it was a two part.

MR. BROOKS: Let me ask you to read the question back.

(Whereupon, a portion of the testimony was read by the court reporter.)

MS. EAGAN: Just for clarification, by medical treatment, you're referring to puberty blockers and hormones; is that correct?

MR. BROOKS: Hormones or surgery, yes.

A. Okay. What judge -- or transitioning treatments for the purpose of this? Okay.

Q. I think we're all on the same page.

A. That's good. So for Part 1, that would be a no. We rely on them to recognize. And by them, I mean MDs or primary providers of pediatric care around the state. The second, yeah. Go ahead.

Q. You finish your answer. I apologize.

A. You're fine. The Part 2 is: Do we always require them to come to us? Let's just say that is not something in our, you know, plans of

care if you make that diagnosis you have to come to us. Does that help? In other words, if someone in the community is working closely with a well-trained psychologist who understands, knows, and works in the space of gender dysphoria, they still need to come to us but we will pick up from there.

Q. Does it ever happen that your clinic prescribes puberty blockers or cross-sex hormones for a minor for whom no mental health professional associated with your clinic has confirmed a diagnosis of gender dysphoria?

A. Can you restate that?

Q. She can read it back.

THE WITNESS: Can you read it back?

(Whereupon, a portion of the testimony was read by the court reporter.)

A. That is not part of our practice parameter. But as I've stated before, there is the occasional case where a youth will come to us

having been under the care of a very well-trained experienced competent Ph.D. psychologist in the community and may arrive with that diagnosis. It will then be also -- there are many other factors that go into prescribing. So, like I said, we will pick up from there. Short answer, no.

Q. In your clinic do you attempt to follow the WPATH Standards of Care --

A. We do.

Q. -- for treatment of adolescents and children?

A. We do.

Q. And have you accordingly made any changes to your procedures since the issuance of WPATH Standards of Care Version 8?

A. No, not formally.

Q. Do you personally diagnose gender dysphoria? Do you personally make diagnoses of gender dysphoria in minors?

A. We do.

Q. My question is you personally?

A. Me personally, in the context of our team setting.

Q. What is your role in the process of diagnosing whether a young person who presents to your clinic does or does not suffer from gender dysphoria?

A. A very robust history with not just the youth but their parents, guardians, household members, those that love them that they bring with them to appointments. We review all records that come to us from the referring primary care doctor as well as mental health professionals that youth may be seeing in community.

Q. My question was: What is your personal role in the diagnostic process?

A. My personal role is to bring out and help my team understand through elevation of the various elements that that youth manifest that may indicate gender dysphoria.

Q. Who within your team or what job description of your team has the responsibility to make the final decision as to whether a child does or does not suffer from gender dysphoria as defined in DSM-5?

A. Our psychologist's view of all of it

weighs heavily, and that must resonate with everyone on the team.

Q. So ultimately with heavy reliance on the psychologist, it's a collective decision?

A. That's fair.

Q. Okay. Do you yourself ever prescribe puberty blockers or cross-sex hormones?

A. Only in the context of youth seen in this team for the purpose of gender dysphoria.

Q. And you yourself in some occasions write that prescription?

A. Sometimes.

Q. Okay.

MR. BROOKS: Let me ask the reporter to mark as Ladinsky Exhibit 2 the transcript of May 5, 2022, one of the days of the preliminary injunction hearing in this matter.

(Whereupon, Ladinsky Exhibit 2 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) And I will tell you

that the days that constitute your testimony -- we have the whole day here, but you don't care too much about most of it. The days that constitute your testimony are behind Tab Number 12.

MS. EAGAN: Is this the redacted version or do we need to put this under the protective order? Because there was one version that's protected under the protective order because of Ms. Poe's testimony.

MR. BROOKS: Ms. Poe's testimony is which pages?

MS. EAGAN: 151 to 170.

MR. BROOKS: Let me have the --

MS. EAGAN: Can we remove those pages?

MR. BROOKS: Let me simplify and remove those pages from the marked exhibit.

MS. EAGAN: If you're just looking at her testimony, can we just mark whatever you put into this notebook that's just her testimony?

MR. BROOKS: Yes.

MS. EAGAN: That will simplify things.

MR. BROOKS: Okay. That's fine.

MS. EAGAN: So why don't we replace what you previously identified as Exhibit 2 with the transcript of just her testimony.

MR. BROOKS: Okay. Remark Exhibit 2.

What we're now marking as Ladinsky Exhibit 2 is a portion of the mini-script transcript from May 5, 2022, including a cover page and then commencing on Page 89 and continuing up to Page 152. That comprising the testimony of Dr. Ladinsky.

(Whereupon, a discussion was held off the record.)

Q. (BY MR. BROOKS) Dr. Ladinsky, I don't want to make this a -- I don't want to waste time going to the transcript all the time. I also don't want to make it a memory test. You testified at the hearing that you had, you said -- and I'm referring to Page 96 if you want to find this -- "Since our clinic's opening, we have

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touched the lives of some 400 to 450 youth." Is that consistent with your recollection generally?
A. That's consistent with my recollection.
Q. And you testified also -- and I quote from Page 128 Line 24. Quote, "No more than a third of them, though, have received medication relative to gender dysphoria."
A. I recall that statement.
Q. And is that generally consistent with your recollection of the facts?
A. It's generally consistent, yes.
Q. And so that takes us to something in the neighborhood of 125 to 150 who over the years have been -- have received medication, either puberty blockers or cross-sex hormones from your clinic; am I correct?
A. That's a fair statement as an approximation, sure.
Q. Do you believe that all of those minors who received puberty blockers or cross-sex hormones from your clinic had, in fact, been diagnosed as suffering from gender dysphoria

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according to the criteria of DSM-5?
A. I believe so.
Q. And does your clinic make an effort to ensure that all minors under their care who are receiving hormones or puberty blockers are also receiving supporting counseling and psychotherapy?
A. We do. It's just not fair to say that as an every single one 100 percent. This is a huge range of youth. But when appropriate, absolutely.
Q. What I asked was: Do you make an effort to ensure that everybody who's receiving puberty blockers or cross-sex hormones is also receiving counseling and psychotherapy?
A. Yes.
Q. Now, the gist of what we've just been through is that two-thirds of those minors who are referred to your clinic do not end up receiving a prescription for puberty blockers or cross-sex hormones; am I right?
A. That's fair.
Q. And why is that? What sorts of situations result in children having enough

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difficulty that they're referred to your clinic but they ultimately don't receive a prescription?
A. There are segments of the youth for whom we see and provide care who are prepubertal. In those younger kids, there's absolutely no indication for any medical treatment or intervention. There's a sizable population of youth presenting to us who are already very far into or have completed a puberty aligned with their natal sex. Those youth are not eligible for medication as well at the time we see them.
Q. Is it your testimony that individuals who have completed puberty aligned with their natal sex are not under any circumstances eligible for cross-sex hormones?
A. They may well be eligible for cross-sex hormones or hormonal therapy with sustained dysphoria and meeting all of the other criteria that our team -- that our team necessitates and mandates before those medications are begun.
Q. Do some young people who come to your clinic who are referred to your clinic, in

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your experience, cease to experience gender dysphoria over -- during the course of counseling and psychotherapy?
A. That's always possible.
Q. Has it happened sometimes? Does that account for some of these children who are referred to your clinic who don't receive a prescription?
A. Good question. For some we'll never know. Some of those 450 may come to see us once and never come back or twice and never come back, and we don't know why. Others -- we have one that I can think of that during the course of work on puberty blockers aligned -- decided in the context of family and therapy that it wasn't necessary.
Q. I appreciate that. That's -- and I recall your testimony about that individual.
Among young people who have been referred to your clinic who have not yet received any prescription for either puberty blockers or cross-sex hormones, does it sometimes happen that in the course of the psychotherapeutic support that your clinic provides or recommends that they

cease to experience gender dysphoria without ever receiving any prescription?
A. It's possible but not to my knowledge.
Q. Okay. Do you have a sense -- let me just take the year 2022 as the most recent completed year -- of what proportion of minors referred to your clinic were natal female versus natal male?
A. I can give you only an approximation, and it matches the approximation of our previous years.
Q. What is that?
A. We see a very close to half/half, very close.
Q. Tab 11. This was your PI declaration, earlier declaration.
MR. BROOKS: I'll ask the reporter to mark this as Exhibit 3.

(Whereupon, Ladinsky Exhibit 3 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) And Dr. Ladinsky, do you recall preparing and signing this declaration prior to the preliminary injunction hearing in this matter?
A. Yes, sir.
Q. In Paragraph 6 -- and this is dated April 20, 2022. In Paragraph 6, you state that, "Since starting at the gender clinic at UAB, I have treated approximately 250 transgender young people for gender dysphoria."
And earlier we looked at testimony in which you had mentioned a number of 400 to 450. Here you said you've treated approximately 250. Can you explain to me what the 250 number represents?
A. At that time it was an approximation of youth that had come through our doors and I believe may have received some form of medication. It was an approximation.
Q. So as the number that have received medication, your testimony now is that it's closer to one-third of that 400ish number; am I correct?

A. That's fair.
Q. And you're going to want to start a stack of paper off to the side somewhere.
MR. BROOKS: Let me mark as Ladinsky Exhibit 4 a set of responses and objections to document request interrogatories served by the University of Alabama System on March 3, 2023.

(Whereupon, Ladinsky Exhibit 4 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, did you play any role in -- to your knowledge, in preparing answers, responses and objections, or just the responses to certain questions on behalf of the University of Alabama System?
A. I played a role.
Q. Without getting into conversations that you had with counsel, would you describe for me what that role was?
A. Of course. Together with my colleague, my partner at the Gender Health Clinic,

UAB Pediatric, Dr. Abdul-Latif, we worked together to provide answers and provide documents to the subpoena request. Also to clarify, especially to counsel, the differences between what's called the UAB Gender Health Clinic where the subpoena was sent, the adult team, as we call it. And a separate multi-disciplinary clinical care team providing care within the UAB Pediatrics Department of Endocrinology.
Q. And just to make sure we're clear on the record, the so-called Gender Health Clinic serves adults; am I correct?
A. It starts at age 18 and up.
Q. Age 18 and up?
A. Yes, sir.
Q. And in Alabama, the legal age of majority is 19 which is different than many states?
A. That's correct.
Q. And the UAB Pediatric Endocrinology Department is the clinic that you are associated --
A. That's correct.

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Q. -- with that serves minors up to --
A. That's correct.
Q. -- the age of 18?
MS. EAGAN: Let him finish his answer before you speak. She has a hard time taking this down.
THE WITNESS: My apologies.
Q. (BY MR. BROOKS) Let me ask you to turn to Page 5 and the objection and response to Number 11. And in this response three lines from the bottom, three, four lines from the bottom, it says, "UAB states that since 2017 the UAB Pediatric Endocrinology Department provided 17 minor patients with puberty blockers and the Gender Health Clinic did not provide any minor patients with puberty blockers." Do you see that?
A. I see that.
Q. Now, earlier you testified that something in the neighborhood of a third of something in the neighborhood of 400 to 450 minors have been treated by the UAB Pediatric Endocrinology Department, if I understand correctly, with either puberty blockers or

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cross-sex hormones, correct?
A. Approximately, yes.
Q. And is it the case -- is it consistent with your knowledge that only 17 of those minors have received puberty blockers?
A. That is correct.
Q. So the overwhelming number of minors who have received any sort of hormonal prescription from your department have received only a prescription for cross-sex hormones?
A. That's fair.
Q. Okay. I just wanted to understand the relationship between those numbers.
And is that reflective of the fact that the overwhelming majority of minors who present at your clinic are already well into puberty at the time you first see them?
A. That is what we see.
Q. Is it fair to say that the majority of minors who present at your clinic are 14 or older the first time you see them?
A. That's a fair statement.
Q. Are the majority 15 or older?

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A. I would not be able to make that distinction for you without --
Q. Okay.
A. -- a records deep dive.
Q. All right. I'm in the right neighborhood, 14 or over?
A. I think that's -- that's the right neighborhood.
Q. In your preliminary injunction declaration which is --
MR. BROOKS: What was the exhibit number on that?
MS. EAGAN: 3.
Q. (BY MR. BROOKS) Let me ask you to turn to Paragraph 11. And there you said, quote, "Most of our patients are in the care of the gender clinic for one to three years before initiating medical treatment for gender dysphoria." Do you see that?
A. I do.
Q. Is that a policy that is written anywhere?
A. I don't believe it's written

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anywhere, but it's very consistent with guideline-driven standards of care longitudinally.
Q. In your professional view, why is it important that patients be in the care and under the observation of your clinic from one to three years before you initiate any medical treatment?
A. Realizing each young person is an individual and is looked at in an individual way. But it's important to -- for us that sustained dysphoria over a longitudinal period of time remains present before initiating such medications. In addition, it gives that youth in the context of, you know, family environment to live in that identity and reflect back from it.
Q. I think you testified that in all of your experience, very few youth who presented with gender dysphoria have desisted from that dysphoria prior to receiving medication, correct?
A. To my knowledge.
Q. And, therefore, why do you believe it to be important to have this extended period of observation before prescribing puberty blockers or cross-sex hormones?

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A. As I said, each youth is unique, and it's very supported of observation not just of the youth but the family. But, again, to ensure to be sure that mental health is optimized, that the youth sustains that dysphoria over a longer period of time.

Q. In your expert report, which is behind Tab 13 in your binder, and is Exhibit Number --

MR. BROOKS: Let me mark as Exhibit 5 the expert report of Dr. Morissa Ladinsky submitted in this matter.

(Whereupon, Ladinsky Exhibit 5 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, you're looking at the copy, which, I believe, is a complete copy in the binder. And do you recognize this as the expert report you prepared and submitted?

A. That's correct.

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Q. Let me ask you to turn to page 11. And there towards the bottom of the page, you wrote, quote, "The WPATH SOC 8 advises that 'it is important to establish the young person has experienced several years of persistent gender diversity/incongruence prior to initiating less reversible treatments such as gender-affirming hormones.'" Closed quote. Do you see that?

A. I do.

MS. EAGAN: I think you said WPATH 7. Should be SOC 8.

MR. BROOKS: Did I say 7? I apologize. It does say 8.

A. There's reference to both in the paragraph, but 8 in the last sentence.

Q. Let me read it again for clarity of the record. Quote, "The WPATH SOC 8 advises that 'it is important to establish the young person has experienced several years of persistent gender diversity/incongruence prior to initiating less reversible treatments such as gender-affirming hormones.'" Closed quote.

In the case of patients who are

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presenting at, for instance, age 14, what steps do you take to ensure that those patients experience several years of persistent gender diversity before your clinic prescribes less reversible treatments such as cross-sex hormones?

A. For clarification, I heard you to say gender diversity. Did you mean that or did you intend to say dysphoria?

Q. I use the term that was in -- that you quoted from WPATH SOC 8.

A. Okay.

Q. I can re-ask the question.

A. I'm just making sure. I got you.

Q. They said gender diversity slash incongruence, and I didn't mean anything different.

A. Perfect. No problem. Thank you. That clarifies it for me.

Q. My question was -- it's been a little while -- what steps do you take to make sure that that patient who walks in the door at age 14 or 15 has experienced several years of persistent gender diversity or incongruence before

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your clinic prescribes any sort of less reversible treatment such as gender-affirming hormones?

A. So that would be obtained -- the first step is a very robust and comprehensive history not just from the youth but the family members or household members that have come to us. We look at records sent from the referring primary care physician or provider as well as taking into account anything that we may have documented or learned from a mental health professional or provider that youth had been seeing in community.

Q. And then, in addition, you, as a general practice, make sure that your clinic sees that youth for at least a year or between one and three years before you prescribe cross-sex hormones?

A. Generally. It depends on the age. This is a 14 year old? Quite likely.

Q. And the reason that you're willing to require several years of observation and mental healthcare before you will prescribe cross-sex hormones is in order to safeguard against something reversible and later regretted mistake;

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am I correct?
MS. EAGAN: Object to the form.
A. That's part of. But I would prefer the term they use right here of "less reversible".
Q. (BY MR. BROOKS) Less reversible than what?
A. What do you mean?
Q. Less is a comparative word. I asked you less reversible than what?
A. Permanent. That was what you said that -- I was just clarifying in WPATH's language.
Q. Do some parents or patients, in your judgment, sometimes walk in the door more certain than they should be that that child needs cross-sex hormones?
A. Great question. And that they should be is probably a value judgment made by -- that may be different for every person in that room. But if we are seeing a youth who may not, you know, fall into our guideline-driven care, that's even more reason for extended support and time with us.
Q. Now, the process of having -- making

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sure the child goes through several years of gender incongruence or gender dysphoria before receiving a hormonal prescription that's advocated by WPATH in the language that you just -- that you quoted in your report may require that child to endure distress as DSM-5 says, clinically significant distress, for an extended period of years before receiving medical treatment; am I right?
MS. EAGAN: Object to the form as to the use of the term "several years of gender dysphoria as opposed to gender diversity."
Q. (BY MR. BROOKS) Are you able to answer my question?
A. If you meant several years of sustained gender dysphoria, I would disagree with that because a youth in that age and stage who manifests gender dysphoria and intense affective possible harmful behavior or thought processes, they will be supported in many different ways through that time both through mental health and through medicine, not including the initiation of hormones, though.

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Q. Ultimately you will decide to prescribe hormones only if you believe that that will relieve distress being suffered by a young person, correct?
A. Among other indicators.
Q. But that's a necessary requirement, correct?
A. An important one.
Q. Is there any circumstance in which you would prescribe cross-sex hormones for a minor where you don't -- where you haven't reached a professional conclusion that that is going to lessen distress suffered by the minor?
A. No, sir.
Q. Okay. Then let me circle back.
A. Okay.
Q. The process of requiring a child to go through several years of gender diversity or incongruence and at least one year of close observation by your clinic before receiving a hormonal prescription means that child will have to endure distress for a significant period before receiving medication; am I right?

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A. No. We don't see it that way.
Q. How am I not right?
A. Well, first and foremost, depending on the age that that youth comes to us, we could stay with the hypothetical 14 year old or extend it to the youth that come to our space for visits. They may be as old as 18. And who may have lived some of this for years before being able to get to us. That's one section. But for youth who, on an ongoing period of work with our team as necessary, they will be very well supported during that time, mental health, possibly other medications.
Q. Other medications appropriate to other mental health indications that you determine this child has?
A. Both that and there are other medications that are used to weigh components of dysphoria. For example, I mean, if you want an example of supportive medication. For a trans male, someone who was female at birth who's through a full female puberty, we can very, very safely reversibly delay menstruation for that person. That's what I meant by supportive

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medication and care.
Q. Is it the experience of your clinic that for these young people who come in diagnosed with or receiving diagnosis of gender dysphoria that you are able to significantly alleviate their suffering during this interim period by means of other medications such as you've described and the mental health support that you've described?
A. Family support, yes.
Q. Let me ask you to turn to Page 16 of your expert report, Exhibit 5. And there at the bottom of the page and running into the next page, it reads, "I prescribe puberty-delaying treatments starting at the Tanner 2 or early Tanner 3 stages of puberty. For people assigned as male at birth, these stages of puberty are typically between ages 9 and 15. And for people assigned female at birth, typically between ages 8 and 13." Do you see that language?
A. I do.
MR. BROOKS: It's Exhibit 5, the expert report submitted.
MS. EAGAN: Thank you.

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Q. (BY MR. BROOKS) Why is the age at which you will initiate puberty blockers for children different for those who are born female than for those who are born male?
A. Remember it's a very individualized decision-making process. And it's based far more upon the physiologic Tanner staging, the physical manifestations of puberty aligned with the natal sex than the age of any individual patient.
Q. Well, Dr. Ladinsky, I started by just quoting language from your report where you noted a typical age difference between when you would begin for someone born female versus someone born male. And my question is: Why that difference?
A. On a population level, the secondary sex characteristic emergence or physical stigma that show us hormonal puberty is starting, right. On a population level, it's earlier for folks assigned female at birth.
Q. And that in your experience is true regardless of their gender identity?
A. Yes.

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Q. And even for earlier maturing patients and taking this on an individual basis, why not nevertheless wait until age 11 or 12 consistent with the original Dutch protocol procedures instead of starting at 8 or 9?
A. If -- like I said, each, you know, each youth is an individual. We have not, in our clinic population, seen the need for what you just hypothetically elucidated in 8- or 9-year-olds. The majority of our youth beginning -- assigned female at birth beginning blockers are 11 or 12.
Q. Why then did you write in your expert report that the stages at which you prescribe are typically between -- begin at age 9 in the case of males and age 8 in the case of females?
A. To reinforce the population level data around entry into puberty.
Q. And, in fact, across the now eight years since you started your clinic, your clinic has prescribed puberty blockers for a grand total of 17 children?
A. That's correct, sir.

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Q. So your clinic experience really doesn't actually even take us to a kind of statistically significant experience and sample; am I right?
MS. EAGAN: Object to the form.
A. I could not answer that. I can only comment on our own experience.
Q. (BY MR. BROOKS) Well, my question had to do with your own experience.
A. Okay.
Q. In your professional judgment, seeing 17 patients who are treated this way across eight years is not a sample large enough to -- from which to draw statistically significant conclusions, is it?
MS. EAGAN: Object to the form.
A. It would completely depend on the question as the population studied. The metrics desired to then calculate what we know as statistical significance.
Q. (BY MR. BROOKS) Have you attempted any systematic study of outcomes for the 17 patients who received puberty blockers from your

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clinic?
A. We have not undertaken or commissioned a systematic study, no. In fact, three of them have relocated out of state under the pressure of this law. It's now 14.
Q. Your clinic has not, as a result of this law, refused to treat any patient, have you?
A. In the way that we had been practicing, that's correct. With the exception of the week that the law was in effect, we most certainly did not undertake anything that would have broken it.
MS. EAGAN: We've been going about an hour. Whenever you get to maybe a stopping point or a change in point, if we could take a short break.
MR. BROOKS: I agree. Let me take us back, and we'll break shortly.
Q. Let me take you again to what's Tab 17 in --
A. I'm sorry. I don't think I have a 17.
Q. You're right. 17 is the responses

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and objections, which is Exhibit 4. I apologize.
Let me take you to the response to Number 15, which is on Page 7. And the very last sentence of this response to Number 15 at the top of Page 7 reads -- sorry. The next to last sentence. "UAB does not track a patient once that patient leaves the care of UAB."
So I just want to ask you about that. What proportion of the patients who enter your clinic do you continue to provide care for through age 18?
A. The majority who -- the majority who continue to return to us and clearly those who are receiving medication.
Q. Of those who have received prescriptions for cross-sex hormones from your clinic, what proportion continued under your care through age 18?
A. The majority unless they relocated out of state.
Q. Well, I'll ask a flip-side question. What proportion of minors received a prescription for cross-sex hormones from your clinic for

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whatever reason terminated contact with your clinic before they reached age 18?
A. None to my knowledge.
Q. None?
A. To my knowledge.
Q. You have had, in your experience, no patients who received prescriptions for cross-sex hormones who are, to use the term, "lost to follow-up" who just ceased contact with your clinic?
A. To my knowledge, no.
Q. Your clinic has been in operation for approximately eight years; am I correct?
A. Correct.
Q. The majority, the substantial majority of patients that you see, you first see at age 14 or 15 or even older, correct?
A. That's correct.
Q. Is it the case that the majority of patients that you have provided prescriptions for over the years have now been adults and outside the care of your clinic for several years?
A. A small cohort, sure. Those that

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were older when we first opened and began and initiated.
Q. Well, those who came in at age 15 just three years ago --
A. Right.
Q. -- are now outside the care of UAB -- I want to use the right term -- Pediatric Endocrinology Department; am I correct?
A. Well, they would be 18 or 19, some. They may be away at college.
Q. The 19-year-olds you don't see. Those are treated in the adult clinic?
A. For the most part. There are exceptions.
Q. Let me take you back to your testimony at the preliminary injunction hearing, which is in the binder, Tab 12.
MR. BROOKS: I'm sorry. We'll take a break that I promised you first.
MS. EAGAN: Okay.

(Whereupon, a brief recess was taken.)

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Q. (BY MR. BROOKS) Let me ask you to take you to the exhibit of your responses and objections to requests of UAB and turn there to Page 6 if you would. And there midway down the page towards the end of the objections and responses to request Number 13, it reads, quote, "Since opening in July 2020, the Gender Health Clinic has conducted one transitioning surgery for an 18-year-old, but no longer provides such treatment to 18-year-olds." Do you see that language?

A. I do see that language, sir.

Q. When was the surgery that's referenced in that response conducted?

A. Sir, I have no knowledge of that because this applies to the Gender Health Clinic at UAB Medicine, what we know as the adult team.

Q. But you have literally no knowledge about this surgery whatsoever?

A. That is correct, sir. I have absolutely no knowledge of this.

Q. Do you know what surgery procedure

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was performed?

A. I do not.

Q. And you don't know when it was performed?

A. No, I do not know that either. That was not performed -- I mean, that was not a patient under the care of the UAB Pediatric Gender Health team of which I'm a part of.

Q. Now, that patient was, in fact, according to this description a minor, 18-year-old. Were you consulted in any way in connection with that patient?

A. I do not recall. That was -- I really don't.

Q. The Gender Health Clinic, the adult clinic was founded in July of 2020 it says. Did you have -- were you consulted in any way in connection with the founding of the Gender Health Clinic?

A. I attended one meeting in -- a good deal before its opening as they were conceiving of it, and they asked my partner and I to attend one meeting long before they opened.

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Q. Okay. The response that I just read includes the statement that the Gender Health Clinic, quote, "no longer provides such treatment to 18-year-olds."

Have you been part of any discussions about that decision to no longer provide such treatment to 18-year-old?

A. No, sir, I'm not. I can only infer they're talking about the law.

Q. Are you aware of any written policy prepared by anyone associated with your clinic or any other part of the UAB medical system, any written policy relating to when surgeries will or will not be provided to legal minors as a treatment for gender dysphoria?

A. I am not.

Q. When did you first become aware that UAB medical system had performed a transition surgery on an 18-year-old?

A. The moment you referred me to this statement.

Q. You never before read this document in its entirety?

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A. No, sir, not -- I don't recall.

Q. And when I read that statement to you, was that inconsistent with what you had previously believed to be true?

A. No.

Q. That is, you previously believed that the UAB Health System had performed surgeries on legal minors as a treatment for gender dysphoria?

A. I was not aware as to whether they were or were not in the particular narrow scope of an 18-year-old. I had no knowledge of policy or action.

Q. Does the Pediatric Endocrinology Department have a policy with respect to recommending surgery for minors as a treatment for gender dysphoria?

A. It is not part of our regular treatment protocol.

Q. Do you have any policy on that written anywhere?

A. I don't believe we have a written policy, but we have a very, very, very long track

record of such.
Q. And why is surgery on minors not part of your protocol?
A. Well, it's currently illegal. But prior to the VCAP law being passed and the surgery section, that being joined, it had not been provided in Alabama nor was it our practice to do such.
Q. And my question is why?
A. We felt -- we align in our thinking very much with the WPATH Standards of Care as well as the Endocrine Society. They do carve out a very, very narrow scope of individually viewing older teens with severe and unrelenting chest dysphoria that they may be candidates for masculinizing chest surgery. That is part of the standards of care and guideline-driven treatment. Beyond that, they do not endorse it and we concur.
MR. BROOKS: Let me mark as Ladinsky 6 the WPATH Standards of Care Version 8.

(Whereupon, Ladinsky Exhibit 6 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) And Dr. Ladinsky, do you recognize this document as a document that you are well familiar with?
A. I'm familiar with it, yes.
Q. Let me ask you to turn to Page 133 or S133 as they number these things for reasons best known to themselves.
MS. EAGAN: Hold on a second. 133?
MR. BROOKS: Yes.
MS. EAGAN: My copy must have missed that.
THE WITNESS: Mine does too. It goes from 120 to something and then 157.
MS. EAGAN: It's missing that part. It goes from 127 to S156.
THE WITNESS: Mine as well.
MR. BROOKS: Never mind.
Q. I'm going to read you -- let me ask you this first, Dr. Ladinsky. You can put that down since it doesn't have the pages I intended.
MS. EAGAN: Can we get a copy if

you're going to start asking questions about a particular section or language. I would like for her to have copy of it to review. I can make a quick copy of it if that's okay.
MR. BROOKS: You can make a copy of this page.
MS. EAGAN: Are you going to ask her about other sections of this?
MR. BROOKS: I don't know that I will. Let's just get that.
MS. EAGAN: It's fine if you want to ask her a question and hand to her.
MR. BROOKS: I'll do that and then we'll mark the page.
Q. When SOC 8 came out, did you make an effort to familiarize yourself with its contents?
A. With relevant sections, yes.
Q. And did you, in fact, participate in any way in the development of the WPATH SOC 8?
A. No, sir.
Q. I'm going to read you a quote from Statement 13.7 on Page S133 and then hand you the text. It says, quote, "We recommend surgeons

consider gender-affirming surgical interventions for eligible transgender and gender diverse adolescents when there is evidence of a multidisciplinary approach that includes mental health and medical professionals has been involved in the decision-making process."
MR. BROOKS: Let me ask the reporter to mark this single page as Ladinsky Exhibit 7 and hand it to her.

(Whereupon, Ladinsky Exhibit 7 was marked and copy of same is attached hereto.)

MR. BROOKS: If you're wanting to identify what section it's in, we do have the table of contents.
MS. EAGAN: It looks like it's not in the section is what she was raising.
MR. BROOKS: That may be the case.
Q. My initial question is: Are you familiar with the recommendation 13.2 that is contained in Exhibit 7?

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A. You mean 13.7?
Q. I do.
A. It aligned with Chapter 13 in its applicability to adults, yes.
Q. Well, do you see the language that I read to you that pertains to adolescents specifically?
A. I do see that. That's correct.
Q. And were you familiar before I showed you this that recommendation from WPATH?
A. I was.
Q. All right. And in the Exhibit 6, let me ask you to turn to Page 66, which I believe you'll find is in the section relating to adolescents. 66.
A. Yeah. Okay.
Q. And there in the first column about 3 inches from the bottom, it says, "Chest masculinization surgery can be considered in minors when clinically and developmentally appropriate."
A. Right here, yeah.
Q. So WPATH, you would agree,

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recommends that chest masculinization surgery can be considered in minors; am I correct?
A. Correct.
Q. And that -- another term for that would be a mastectomy. It's removal of the breasts of a natal female; am I correct?
A. I'm not a surgeon to comment on that exact detail.
Q. You are a doctor. Do you understand the surgery that's referred to to consist of removing the female breasts?
A. Yes.
Q. And let me ask you to look at second column on the same page.
A. Okay.
Q. And about 2 inches down is a sentence that begins, "Limited data are available on the outcomes for youth undergoing vaginoplasty." Do you see that?
A. I do, yes.
Q. And a little farther below it says, While the sample sizes are small, these studies suggest there may be benefit for some adolescents

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to having these procedures -- that is vaginoplasty -- performed before the age of 18. Do you see that?
A. I see that.
Q. And am I correct -- do you have an understanding of what vaginoplasty as the term is used by WPATH refers to?
A. I do.
Q. It's a procedure performed on natal males; am I correct?
A. Correct.
Q. And it includes --
A. In this context.
Q. -- removal of the penis?
A. That's correct.
Q. And it includes castration; am I correct?
A. I believe so.
Q. And it is, in your understanding, absolutely and completely irreversible, is it not?
A. I view it that way.
Q. And you were aware, were you not, that WPATH says that that surgery may be

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appropriate before age 18?
MS. EAGAN: Object to the form.
A. I'm seeing it in front of me here.
Q. (BY MR. BROOKS) Well, you testified earlier that once the Standards of Care 8 came out, you took care to familiarize yourself with the sections dealing with adolescent health, right?
A. Correct.
Q. And you were aware before you sat down for this deposition today that WPATH is stating to the world that this procedure, including castration and removal of the penis, may be appropriate for natal males younger than 18?
A. That is what they're saying right here.
Q. And you were aware of that shortly after the Standards of Care 8 came out; am I right?
A. Aware, yes.
MR. BROOKS: Let me mark as Ladinsky Exhibit 8 the Endocrine Society --
MS. EAGAN: Hold on one second,

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Roger.
A. This is what I take with me when I review this chapter, the line just a few sentence -- at the end of that long paragraph on the right-hand side. Given the complexity -- da, da, da -- "it is not recommended this surgery be considered in youth under 18 at this time."
Q. (BY MR. BROOKS) And then it says, "see Chapter 13-Surgery and Postoperative Care," correct?
A. Correct.
Q. And earlier I directed your attention to language in Chapter 13, correct, where we discussed the recommendation to surgeons. Do you recall that language?
A. I do.
Q. All right.
MR. BROOKS: Let me mark as Ladinsky Exhibit 8, the Endocrine Society Guidelines 2017 edition. This is in your binder behind Tab 37.

(Whereupon, Ladinsky Exhibit 8 was marked and copy of same is attached

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hereto.)

Q. (BY MR. BROOKS) Let me call your attention -- and I should ask: Is this a document that you consider yourself to be well familiar with?
A. I'm familiar with it, yes.
Q. And have you consulted it with some regularity in your practice since it issued in 2017?
A. We're aware of it, yes.
Q. Is it a document that you rely on as an important source of standards in your profession?
A. It's an important document, yes.
Q. Let me ask you to turn to 3894. I see you checking the section heading, which is appropriate. 2 inches from the bottom of the first column of 3894, it reads, quote, "Because some transgender male adolescents present after significant breast development has occurred, they may also consider mastectomy two years after they begin androgen therapy and before age 18 years."

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Closed quote. Do you see that?
A. I do see that.
Q. And in fact many of the natal females who present at your clinic have already experienced significant breast development; am I correct?
A. That's correct.
Q. And therefore according to the Endocrine Society Guidelines, they would be candidates for mastectomy before the age of 18?
A. The endocrine -- the guidelines suggest that, yes, it may be considered for that narrow population.
Q. Dr. Ladinsky, you actually described that in your other testimony not as a narrow population but as the primary population presenting at your clinic; am I correct?
MS. EAGAN: Object to the form.
A. By narrow, sir, I meant the small group of older teens assigned female at birth.
Q. (BY MR. BROOKS) Let's be clear. Most girls by age 14 have some significant breast development, correct?

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A. That's fair.
Q. And I believe you've testified that the majority of girls consenting at your clinic are 14 or older when you first see them?
A. That's true.
Q. And therefore it follows that majority of girls who present at your clinic, according to the Endocrine Society Guidelines, are candidates for mastectomy before age 18, correct?
A. If you read it as such.
Q. Do you read it differently?
A. It simply says may be considered. The clinician should individualize treatment based on the physical and mental health status of the individual. It's a guideline. Yeah.
Q. Are you aware of any guidelines that you consider to be respected in your field that do not approve mastectomies for natal females younger than 18?
A. I am not.
Q. And yet in your clinic, you do not perform or refer natal females for mastectomies younger than 18, correct?

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A. Correct.
Q. Is that because you disagree with the medical views expressed by WPATH and the Endocrine Society?
A. No, sir, does not.
Q. Do you think it is appropriate or inappropriate to perform mastectomies on minors?
A. Are you asking for my opinion?
Q. Yes. You're an expert offering opinion evidence.
A. I think the guidelines read very accurately and very fairly in that there is a small group of older teens assigned female at birth who manifest severe chest related dysphoria. And for those teens, I agree with the guidelines that it could be considered.
Q. But you don't consider it in your clinic and you never have?
A. Consider is a relative term. Is it discussed? At times when patients bring that up. The procedure itself has not been assessable in the state of Alabama and is now illegal.
Q. To your knowledge, clinics in

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multiple states are in fact performing irreversible mastectomies on natal females under the age of 18 in numerous cases each year, correct?
MS. EAGAN: Object to the form.
A. I could not comment on the numerous part of it. I don't know how many are being performed in centers around the country, but I am aware that that does occur.
Q. (BY MR. BROOKS) Well, based on your reading the literature and your conversation with colleagues, you are aware, are you not, that mastectomies are being performed on hundreds of girls around the country each year as a treatment for gender dysphoria?
MS. EAGAN: Object to the form.
A. Again, I could not comment on numbers, sir.
Q. (BY MR. BROOKS) You have no knowledge?
A. I don't have knowledge of numbers. I'm aware it happens.
Q. If the Endocrine Society and WPATH

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recommend that mastectomies be considered as a treatment for natal females who are minors, do you think it's medically reasonable for your clinic to never approve such procedures among your several hundred patients?
MS. EAGAN: Object to the form.
A. I mean, the guidelines speak to a very, very small group of exception, older trans masculine teenagers. Now to your question, it's never been part and parcel of the surgical work performed at my hospital, and my hospital is the only tertiary referral hospital in the state of Alabama.
Q. Have you ever referred a natal female for chest surgery to a medical center outside of Alabama?
A. Tell me what you mean by refer.
Q. Well, let me ask you if that is a term that has a technical meaning to you as a doctor?
A. It does.
Q. What does it mean to you?
A. As a primary care doctor, it means

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we are identifying and securing for the patient the source of care, and then we're discussing with the accepting physician, providing records and such, et cetera. So that is -- no, it has not been part of our practice to do so in that way.
Q. You have not done that?
A. I have not, sir, no.
Q. Okay. Let me ask you to find your transcript from the preliminary injunction hearing, which is 12. It's in the binder. Tab 12, your transcript.
MS. EAGAN: Did you say a page?
MR. BROOKS: I didn't yet.
Q. I'm going to direct your attention to Page 122.
A. I don't have 122.
MS. EAGAN: Here.
Q. (BY MR. BROOKS) I'll regularly refer only to the little page numbers. If you look at Line 22.
A. Okay.
Q. You were asked, "Did you review any studies or literature reviews or other research in

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putting together the declaration?" Referring to your PI declaration. And you respond, "We're continually doing that. It's part of our job." Do you see that testimony?

A. I do see that.

Q. Can you describe for me the steps you take to make sure that you are continually reviewing and current with the literature in your field?

A. Sure. The steps we take are this: We're always reviewing and re-reviewing guidelines. So, for example, the WPATH SOC 8, which are fairly new, so there's review of those as it pertains to patients we care for. There's continually reading published studies in this area. As well as national meetings and conferences where we're discussing with colleagues.

Q. And the guidelines -- so, for instance, the WPATH SOC 7 came out in 2012, correct?

A. Correct.

Q. So it was 11 years between Version 7

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and Version 8; am I correct?

A. Roughly. A decade apart.

Q. So the guidelines wouldn't necessary make you aware of the latest research in your field, would they?

A. Not necessarily because findings or studies may be published subsequent to it.

Q. And the Endocrine Society Guidelines, the current version, was published in 2017, correct?

A. Correct.

Q. How do you go about making sure that you are identifying and reading important new research papers in your field?

A. Those of us that do this work are united on multiple different lists. As colleagues, we're always elevating for each other anything new that may have come out. So we work as a team throughout the nation.

Q. Let me ask you to find your CV, which is Exhibit 1. Let me ask you to turn to Page 8.

A. Okay.

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Q. And there you listed major research interests. Do you see that?

A. Yes, sir.

Q. Nothing relating to the effects of puberty blocker or hormones on the body or brain of children or adolescents is one of your major research interests, correct?

A. That's correct.

Q. And nothing relating to the long-term physical and mental health outcomes of children or adolescents who are subjected to puberty blockers or cross-sex hormones are among your research interest, correct?

A. Very interested in them, but I'm not doing that research myself.

Q. If you turn to Page 11, again it's a list of manuscripts. And just to avoid any confusion, by manuscripts, do you mean papers submitted to peer-reviewed journals?

A. Papers published in peer-reviewed journals.

Q. You don't have any peer-reviewed paper that relate to any issue of transgender

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medicine, diagnosis, therapy, or outcomes, do you?

A. That's correct. I'm not a researcher. I'm a clinician.

Q. Let me ask you to look again at your transcript, Tab 12, and turn with me to Page 121 if you would. And at 121 beginning at Line 9, you testified, quote, "An experimental treatment will be a drug or a medical intervention that is part of a very, very tightly controlled clinical trial, a trial that has been granted, you know, granted a yes or no, granted the ability to do so by an institutional review board which strictly upholds the ethical rights of human subjects." Closed quote. Have I read that more or less correctly?

A. You have.

Q. Are you familiar with the term "case study"?

A. I am.

Q. And do you consider a case study to report on, in some cases, to report on an experimental treatment?

A. Not generally.

Q. Based on your definition of

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experimental treatment as given in your preliminary injunction testimony, am I correct that you yourself in the course of your work at the UAB Pediatric Clinic have never engaged in any experimental treatments?

A. As defined in this way, that's fair.

Q. And you have never in fact undertaken any experimental work in the field of pediatric treatment of gender dysphoria?

A. Personally, no.

Q. Have any of your colleagues, to your knowledge, at UAB participated in any experimental work relating to treatment of minors for gender dysphoria?

A. I'm not aware of that.

Q. You would agree, would you not, that before full clinical trials are undertaken that clinicians may in some cases try novel drugs or therapies on individual patients separate and apart from a tightly controlled clinical trial?

MS. EAGAN: Object to the form.

A. I'm not sure what you mean.

Q. (BY MR. BROOKS) In some cases,

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drugs that have not been subjected to a formal clinical trial are nevertheless prescribed to patients on an experimental basis, would you agree?

A. I'm not sure I use the word "experimental" in the same way, though. That's where I'm getting stuck.

Q. Well, if it hasn't -- if a drug has not been proven to be efficacious or it has not been proven to be safe, wouldn't you agree that its use on a human subject is experimental?

MS. EAGAN: Object to the form.

A. I don't know that we use the -- we don't use the word "experimental" in that way.

Q. (BY MR. BROOKS) That would be more pre-experimental?

A. No. I've not heard that term either.

Q. Well, when a drug is used in a context for which the type of formal experiment you described in your testimony has not yet been done, we don't have that information. We don't have the results of that type of carefully

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controlled clinical trial. How would you describe -- what terms would you use to describe that usage of the thus far untested pharmaceutical?

A. Well, it's not part and parcel of my regular practice, but I would assume that a medical provider engaging in what you describe would first and foremost explain to the patient and family in a detailed way what is known, what may not be known, and what they hope to achieve and how they will monitor for it.

Q. Well, my question for you is: What term would you use for the use of a drug for an indication or in a population for which it has not yet been tested and proven efficacious through the type of very, very careful clinical trial that you described in your testimony?

A. I think clinicians have a variety of terms if they're engaging in this that they would use. It's not part of my regular practice.

Q. What do you consider to be terms that clinicians would use for that type of use prior to proof of efficacy through a carefully

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controlled clinical trial?

A. I think the word that would come to mind would be novel.

Q. Do you know whether any of your colleagues at UAB are currently enrolling minors in any experimental research relating to treatment of gender dysphoria?

A. I'm not aware. That doesn't mean it's not happening in other divisions.

Q. Let me ask you to find your expert report, which is 5. Let me ask to you turn to Page 21. At the top of Page 21, you write in your expert report, quote, "In addition to my patients with intersex traits, I regularly manage non-transgender patients receiving the same hormones that are provided to transgender patients." Closed quote.

Given that you're not an endocrinologist, can you describe to me your professional responsibilities at UAB associated with non-transgender patients and the administration of hormones?

A. I'm a primary care pediatrician, and

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I see patients as well as teach in our pediatric primary care clinic. So we have adolescents who may have indications for hormonal therapy for reasons that -- for indications that don't involve gender dysphoria. Patients in that top paragraph, hypogonadotropic hypogonadism, the endocrinologist may have those patients on hormonal therapy. As a primary care physician, I am sort of -- I'm their, you know, I have a deep understanding of the medication and am helping endocrinology monitor for, you know, for that.

Q. You yourself have never prescribed hormones for any non-transgender patient; am I correct?

A. What do you mean by -- like right here, hormonal birth control?

Q. Well, let me be more specific.

A. Okay.

Q. You yourself have never prescribed testosterone suppression for any non-transgender patient, correct?

A. I have not.

Q. And you yourself have not prescribed

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estrogen for non-transgender girls for the type of use that you describe in the middle of that paragraph?

A. For which use, the hypothalamic, pituitary issues?

Q. I'm glad you said that. You say, and I'll quote, "For example, non-transgender girls with hypogonadotropic hypogonadism (delayed puberty due to lack of estrogen caused by a problem with the pituitary gland or hypothalamus) may be treated with estrogen to initiate puberty." Closed quote. Have I read that accurately?

A. You have.

Q. And have you yourself ever prescribed estrogen to a non-transgender girl for that purpose?

A. For that indication, I have not. But I do help manage them.

Q. What do you mean by manage?

A. As a primary care physician, we see our patients fairly frequently, and they know how to find us. So I will continue to review potential side effects, potential

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contraindications. I see you're taking estrogen, we're not smoking or vaping, that kind of thing. That's what I mean.

Q. You don't consider yourself a specialist in intersex conditions, do you?

A. I do not.

Q. And, indeed, that is not a topic on which you've ever made any publications, correct?

A. No, sir.

Q. Nor have you ever given a presentation on intersex condition at any professional meeting, am I correct?

A. Not on that as a primary reason, no.

Q. Colleagues do not consult you for your expertise in intersex conditions, correct?

A. No, sir. Not for the medical management of them.

Q. How much of your professional time -- you've mentioned that you have a role as a primary care physician?

A. Correct.

Q. How much of your professional life is occupied with your work with the UAB Gender

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Clinic?

A. Percentage? Fraction? Which would you like me to?

Q. Whatever you're comfortable with.

A. Maybe 25 percent.

Q. And do you receive separately identified compensation from the UAB System in connection with your work with the Gender Clinic?

A. No, sir. I'm salaried.

Q. And within the last five years, have you received any other compensation beyond your UAB salary of any sort related to gender dysphoria or treatment for gender dysphoria?

A. Not for medical management or anything thereof.

Q. Have you received speaker fees for talks given on that topic?

A. I think I once got a $25 honorarium.

Q. Have you received any sort of compensation or reimbursement for any pharmaceutical company relating to treatment for gender dysphoria?

A. No, sir.

Q. You were named as a plaintiff in a lawsuit in 2022: Ladinsky versus Ivy, correct?
A. Correct.
Q. And did you carefully review the complaint in that action and satisfy yourself that everything in it that fell within your scope of knowledge was true and correct?
A. I believe so.
Q. In that lawsuit, you were not attempting to fill the role of a disinterested and impartial expert, but rather you were a plaintiff personally suing the State of Alabama; am I correct?
A. That's correct.
MR. BROOKS: Let me mark as Ladinsky Exhibit 9 a press release that appears to be dated March 8, 2021. Titled City of Birmingham's LGBTQ plus Advisory Board Issues Statement on HB1/SB10.

(Whereupon, Ladinsky Exhibit 9 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, do you recognize this document?
A. I do.
Q. I see that your name is the first of several signators?
A. Correct.
Q. Are you the primary draftsman of the document?
A. One of them. The first reviewer.
Q. Who was the initial drafter?
A. That's an excellent question. I believe it was one or a combination of my colleagues on the mayor's task force advisory firm.
Q. Who specifically?
MS. EAGAN: If you remember.
A. Yeah, I don't recall.
Q. (BY MR. BROOKS) That's always a fine answer.
MS. EAGAN: It's the truth.
A. It is the truth. That was a few years back.
Q. (BY MR. BROOKS) I understand.

Towards the bottom of the text, the sentence that reads, quote, "The medicine in question follows a standardized evidence-based gender affirmative model of pediatric care." Do you see that?
A. I do.
Q. Can you explain to me what you understand the term "evidence-based" to mean?
A. Meaning simply consensus bodies of experts in the area have and are continually reviewing the best available evidence in the issue standards of care guidelines for practice and are continually reviewing and revising them.
Q. Do you understand evidence-based to be a term of art?
A. I do not. I've not viewed it that way.
Q. Have you ever received any training in what is referred to formally as evidence-based medicine?
A. I have.
Q. And describe to me the context in which you've received that training.
A. Through not just my medical training

but more so during my fellowship training. We work with -- we spent a lot of time in the distillation of different studies, validity consistency, how to read the literature and understand science in the most empirical form relative to the issue in question.
Q. Are you aware that there is now a whole field developed of evidence-based medicine?
A. I am aware of that.
Q. And do you believe you have an understanding of how evidence-based medicine is defined within that field?
A. I will -- I have an understanding of it, but I could not give you the exact verbiage of their vision and how they see it.
Q. You continue in the sentence that -- I read a partial sentence into the record, and it continues that this model of pediatric care is, quote, "endorsed by the American Academy of Pediatrics and its 67,000 members nationwide." Closed quote. Do you see that language?
A. I do.
Q. Is it your understanding that the

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AAP membership, which you refer to, was ever given any opportunity to vote on any standard or statement relating to medical care for gender dysphoria in minors?

A. I believe there are processes that involve that.

Q. You believe there was a process that involved an opportunity for the entire membership of the AAP to vote on whether or not to endorse any statement or standard relating to medical care of gender dysphoria in minors?

A. The process does not, you know, does not solicit individual votes from all 67,000 members prior to the issuance of a policy statement or a set of guidelines. However, there are processes that entail the ability for feedback and for local regional, you know, executive leadership in so many domains to bring that input. It's sort of a small democracy basically.

Q. But a democracy in which the 67,000 members that you refer to never get an opportunity to vote, correct?

A. Through their sections councils, et

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cetera. They don't, you know, take a vote on every single policy statement, but they are given time to elevate input and questions, absolutely.

Q. You stated in the previous paragraph that, quote, "The bill further demands that school personnel out students who are trans or gender-diverse to their parents or guardians." Closed quote. Do you see that?

A. I do see that.

Q. And am I to understand that you support policies under which a child's adult authority figures at school may actively participate in a social transition of a child without first obtaining parental consent?

MS. EAGAN: Object to the form.

A. Tell me what you mean by participate in a transition.

Q. (BY MR. BROOKS) Sure. Addressing a child with a transgender name or cross-sex pronoun, for example.

A. Okay. Now tell me your question relative to that.

Q. Should I take it from the statement

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in this press release from 2021 that you support policies under which a child's adult authority figures at school may actively participate in the social transition of a child without first informing the child's parents and obtaining parental consent?

MS. EAGAN: Object to the form.

A. I'm not sure I can answer it in the way that you've asked it. I think the sentence gets to the heart of what could be a safety issue for some students in Alabama.

Q. (BY MR. BROOKS) Dr. Ladinsky, do you or do you not believe that schools in Alabama should be permitted to actively participate in the transition of children without the consent of their parents?

A. I'm confused by this actively participate in the transition --

Q. I explained what I meant by that because you asked me for an explanation.

A. Because I don't see that -- I don't see that the same as simply affirming a child or an adolescent in the school setting in the name or

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identity they've asked to be identified with.

Q. Then let me make my question more precise.

A. Okay.

Q. Do you or do you not believe that schools in Alabama should have policies that allow the child's adult authority figures at school to participate in the social transition of a child by addressing the child with a cross-sex name or pronouns without first obtaining parental consent?

A. I believe that lies within the purview of educators in that school, period. They know what's best for their youth.

Q. Your testimony here today is that it's your professional opinion that the educators in this field of gender dysphoria know what's best for youth more than the parents?

MS. EAGAN: Object to the form.

A. No, sir.

MS. EAGAN: Misstates her testimony.

A. No, that is not my testimony at all.

Q. (BY MR. BROOKS) Then explain better what you just tried to tell me.

A. What I meant to say is that it is purview of the schools, the district, the school setting to set policy relative to how educators address and possibly affirm students.

MR. BROOKS: I'd like to mark as Ladinsky Exhibit 10 an excerpted chapter from a book entitled "Users' Guide to the Medical Literature, Essentials of Evidence-Based Clinical Practice" by Gordon Guyatt and others, Third Edition.

(Whereupon, Ladinsky Exhibit 10 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, let me first ask whether you're at all familiar with the name and reputation of Dr. Gordon Guyatt?

A. I'm not.

Q. And let me ask whether you have ever seen this book in any edition: Essentials of Evidence-Based Clinical Practice?

A. I have not.

Q. Have you ever attended -- taken a course or attended a seminar in principles of formal evidence-based clinical practice?

A. I have not.

Q. Let me ask you to turn to Page 15. And there Figure 2.3 or 2 dash 3 is headed Hierarchy of Evidence. And let me ask whether you believe you have any familiarity with the concept of a hierarchy of evidence as a characteristic of evidence-based medicine?

A. I'm familiar with that.

Q. And when you look at Figure 2-3, are these categories of evidence that you believe you understand?

A. Yes.

Q. What do you understand the observational study to be?

A. When a researcher identifies a sort of new population of patients or patients with a specific entity or characteristic and also metrics that would underlie patient important outcomes. They follow that group for a period of time.

Q. And what do you understand to be the

difference between an observational study and a multi-patient randomized trial?

A. Both would be to an extent prospective, meaning they start at time zero and study population going forward. However, the second one, the randomized trial assumes what they call equipoise, meaning that if you're looking at the -- wondering about outcomes relative to this population, we really do not know that an intervention or that an outcome can be modified by something. We want to find out. And so you would randomly select, and there are procedures for that. In a randomized trial, two different groups of patients, following them forward.

Q. Are you able to explain why a multi-patient randomized trial ranks higher in the hierarchy of quality of evidence than an observational study?

A. Because when you have two different groups whose characteristics are tightly controlled from the beginning, it's easier to factor out what we call preponderance or extraneous factors impacting your metrics, what

you want to learn about at the end.

Q. Let me ask -- were you finished?

A. Yes, sir.

Q. Let me ask you to turn to -- it's a long preface. If you would turn to Page 27 in the preface.

A. Here's 27.

Q. We're going to -- so if you look earlier in the preface, you will find Roman numerals pagination rather than arabic. And I said 27, but I meant 26.

A. Okay. I'm confused. We're going back to Roman numeral areas?

Q. Yes, we are.

A. Okay. So that's going to be closer to the beginning.

Q. It is. Page 26. And there's a paragraph I want you to read that begins, "Awareness of the importance of the pre-appraised evidence and evidence-based recommendations." And then it says, quote, "We have added a fundamental principle to the hierarchy of evidence and the necessity for value and preference judgments: that

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optimal clinical decision-making requires systematic summaries of the best available evidence."

A. Okay.

Q. Are you familiar with the concept of systematic review of medical evidence in your field?

A. I am. Not in a, you know, deep dive detailed researcher way, but yes.

Q. Have you ever participated in performing a systematic review?

A. No, I have not.

Q. Have you ever had occasion to carefully study a systematic review done by some outfit or group of analysts?

A. I've certainly read them.

Q. Are you able to tell me as you sit here today any specific systematic reviews relating to literature relevant to your field that you have consulted?

A. Explicitly, not -- I mean, the guideline documents themselves include systematic reviews, and there are papers and a number of

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papers on literature relative to the topic at hand that include this as part of what they're discussing.

Q. Is your understanding that the Endocrine Society Guidelines themselves include or -- include a systematic review?

A. I believe that's incorporated into it.

Q. Have you ever consulted the systematic review that you believe those guidelines made use of?

A. I've not explicitly reviewed every single one.

Q. Have you explicitly reviewed a single systematic review relied on by the Endocrine Society 2017 Guidelines?

A. I would have to go back and look at the guidelines to see which ones they referenced and cross it with which ones I read.

Q. And do you know, as you sit here today, whether in comparing WPATH SOC 8, WPATH, or anybody associated with WPATH performed any systematic guideline of any systematic review of

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literature on any topic?

A. I do not explicitly know the answer to that question.

Q. A little father down in the paragraph that begins, "This principle has led," is a reference to GRADE, G-R-A-D-E, Grading of Recommendations Assessment, Development, and Evaluation. At which it refers to as providing, quote, "an assessment of the confidence that one can place in the estimates of effect emerging from the review and meta-analysis."

Are you familiar with the GRADE system of evaluating the strength of evidence?

A. I'm familiar with it, yes.

Q. And have you ever received any training in how to apply the GRADE system to evaluate the strength of particular published evidence?

A. Not formally but it is part and parcel of the work that we do as clinicians and especially as educators in academic centers.

Q. Have you yourself ever attempted to apply the criteria specified by the GRADE system

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to arrive at a conclusion about the reliability of a particular experimental result reported in the literature?

A. I take it into account as I read each recommendation, yes.

Q. You believe that you are on an ongoing basis familiar with the criteria specified in the GRADE system for evaluating strength of evidence?

A. I'm familiar with it. It's generally reviewed to in studies.

Q. On Page 15 of this document, which I had you look at Figure 2-3 on previously. Page 15.

A. Okay.

Q. It reads toward the bottom of the page, quote, EBM, evidence-based medicine, places the unsystematic observations of individual clinicians lowest on the hierarchy. Closed quote. Do you see that language?

A. I do.

Q. Is it consistent with your professional understanding that the unsystematic

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observations of an individual clinician such as yourself is the least reliable form of evidence?
MS. EAGAN: Object to the form.
A. I would infer they are referring to a published case report or case collection in the literature, not my own personal commentary or observation.
Q. (BY MR. BROOKS) Is it your opinion that your own personal unpublished observation is a more reliable source of evidence than published observations of clinicians?
MS. EAGAN: Object to the form.
A. I don't think that plays into what is being discussed in this document. This is about medical literature and a hierarchy of study design.
Q. (BY MR. BROOKS) And in the hierarchy of evidence in Figure 2-3, clinical experience is the lowest least reliable form of evidence; am I correct?
A. In the setting in which they describe study design and type, that is what they've got here.

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Q. And is it consistent with your understanding as a scientist that clinical experience is the least -- provides the least reliable evidence when it comes to potential treatments and outcomes?
MS. EAGAN: Object to the form.
A. I don't think the clinical experience of one clinician plays into what they're evaluating here. How to understand evidence is presented in a formal published study or a prospective trial.
Q. (BY MR. BROOKS) And why is it that you don't believe that the clinical experience of an individual clinician such as yourself fits into the hierarchy of evidence specified by evidence-based medicine and principles?
A. Because I think -- it's my impression in this context, having not read the document, but in this context, that they refer to clinical experience -- right here, "either your own or that of a colleague." As a reference point to understand evidence there all the way up to what you refer to as a randomized trial.

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Q. In fact, it's your understanding, is it not, that opinions and clinical decisions simply based on a clinician's experience is exactly the problem that evidence-based medicine was developed to solve?
A. I do not know the answer.
Q. In the seven or now eight years since UAB Pediatric Gender Clinic was founded, your clinic has never published -- no one associated with your clinic has published any systematic observational studies of the outcomes in children as a function of the selection or timing of treatment options, correct?
A. That's correct.
Q. And you don't cite anywhere in your report any quantitative data from your own clinic or your own years of experience practicing in this field, correct?
A. Correct.
Q. You don't cite anywhere in your report any systematic review of literature relating to your field, do you?
A. I'd have to look back to see. I

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know that there are references in some.
Q. You know that there are references to systematic reviews in your expert report?
A. I would have to look back at the many, many that -- the studies that I referenced there.
Q. Did you make an effort to identify relevant systematic reviews of evidence relevant to your field in the course of preparing your expert report?
A. I believe so.
Q. You would agree, would you not, that the seminal and most cited research relating to the treatment of gender dysphoria in minors came out of the Netherlands and Vrije University research team in particular?
A. The earliest ones leaned on the foundation for care provided, yes.
Q. And prominent researchers and clinicians associated with that clinic include Dr. Cohen-Kettenis, Dr. de Vries, Dr. Steensma, Dr. van Goran, correct?
A. I know those names, yes.

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Q. Over the years you've read many papers published by researchers associated with the Vrije University clinic, have you not?
A. Several.
Q. Is it consistent with your understanding that that university team is the most respected source of research in your field in the world?
A. I think that's a subjective question.
Q. It is, and I asked your opinion.
A. I never -- I mean, are they highly respected, absolutely. Are they highly experienced, absolutely.
Q. And important publications are still being put out by the Vrije University research team up to the present, correct?
A. Correct.
Q. And they're published in English to your knowledge, right?
A. Those that I've read certainly are.
Q. Have you met any of these four doctors that I just mentioned at conferences or

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any professional context?
A. I have not.
Q. As part of the continual work that you mention to stay current in research relating to the treatment of gender dysphoria in minors, you attempt to stay abreast of publications from the Vrije University research team, do you not?
A. I do my best.
Q. It's not your opinion that peer-reviewed research coming out of Europe is somehow less relevant to you as an American doctor, is it?
A. Tell me what you mean by less relevant. Do you mean unimportant or not relevant to what I do?
Q. Is it your opinion that peer-reviewed research coming out of Europe is somehow less relevant to your clinical decision-making than research coming from American researchers?
A. It would depend on the topic being evaluated. If they're looking purely at systems of care, possibly. But if they're looking at

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valid results of certain elements of care, possibly. Of course we're going to take that into strong consideration.
Q. In fact, it continues to be the case that much of the important research relevant to your practice as a clinician comes from European authors, is it not?
A. I can't agree with that statement.
Q. No. Is it your opinion that the bodies of children in Europe respond differently to puberty blockers or cross-sex hormones than the bodies of children in America?
A. I can't imagine that being a truthful statement.
Q. And likewise, it's not your opinion that the minds of children in Europe would respond differently to puberty blockers or cross-sex hormones than the minds of children in America?
A. It's a pretty absolute statement with subjectivity. It's confusing. They're different environments.
Q. Well, is it your opinion that the minds of children in Europe respond differently to

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puberty blockers or cross-sex hormones than the minds of children in America?
A. I have not seen evidence to that.
Q. Of any such difference?
A. Correct.
Q. You would agree, would you not, that any responsible clinician needs to stay current on the latest research results and systematic analysis from North America, Europe, and the UK?
MS. EAGAN: Object to the form.
A. I agree they should -- all of us do our best to stay current with relevant research. We also do so with an eye to the various factors that impact the patients including the study.
Q. (BY MR. BROOKS) Are you aware of the Karolinska Institute in Sweden as a respected source of research in your field?
A. I've heard of such.
Q. Are you familiar with a Dr. -- I'm not going to say her name correctly -- D-h-e-j-n-e, Dhejne as a researcher whose literature you have seen?
A. I've seen that name.

Q. Are you aware that another author with a substantial number of peer-reviewed papers relating to treatment of gender dysphoria in children is Professor Michael Biggs of Oxford University?
A. I'm not aware of that name, no.
Q. Let me take you to the Endocrine Society Guidelines which are tab 37 in your binder and Exhibit 8 and ask you to turn to Page 3872. Do you have 3872?
A. I do.
Q. Column 2. Down below the heading Method of Development.
A. Okay.
Q. It states five lines down, the task -- quote, "The task force followed the approach recommended by the Grading of Recommendation, Assessments, Development, and Evaluation group." GRADE. And it says a little farther down, "The task force used the best available research evidence to develop the recommendations." Do you see that?
A. Correct.

Q. Do you know whether the Endocrine Society either -- whether the authors, I should say, of these guidelines, either performed or commissioned any systematic review of available science in connection with preparing the guidelines?
A. I would hope so.
Q. Do you know whether they did?
A. In the way that you're defining it, I don't. Right here it talks about it, though. "The task force commissioned two systematic reviews to support this guideline."
Q. Do you know what the subject of those two systematic reviews was? And I don't -- I'm not -- I don't want to trick you. There is a description --
A. It's right here.
Q. -- 3873 if you look in Column 1.
A. Right.
MS. EAGAN: Take the time to read that. If he's going to ask you questions about this commissioned systematic review, take your time if you need to and read through it, Dr. Ladinsky.
THE WITNESS: I will.
A. Just this section, sir, commissioned systematic review?
Q. (BY MR. BROOKS) I understand that to be the paragraph that you just read to be a description of the two systematic reviews that are referred to.
A. Well, right here --
MS. EAGAN: I'm not sure there is a question, though, on the table.
Q. (BY MR. BROOKS) And let me -- before calling your attention to this paragraph, did you have any recollection as to what the Endocrine Society had sought systematic reviews of?
A. It was my impression there were several different entities within this field.
Q. And what this paragraph tells us is that there was, quote, first review that focused on the effect, quote, the effect of steroid use in transgender individuals on the cardiovascular outcomes, correct?

A. That's what it says.
Q. And at the top of the next column, it says that, "The second review summarized the available evidence regarding the effect of sex steroids on bone health in transgender individuals."
Do you have an understanding of how lipids and cardiovascular outcomes are potentially relevant to your field?
A. I do as in long-term risk factors, but I would be curious as to -- I would want to know the populations involved here. Were these adults?
Q. Do you have an understanding of what relevance bone health has to your field?
A. Of course.
Q. And what is that relevance?
A. That relevance is the laying down and then retaining supporting of bone mineral density, the strength of the cortical bone.
Q. And why is that an issue of potential concern in connection with treatment of transgender individuals?

A. Any time you're discussing a hormonal impact relative to adolescents, bone density may be involved.
Q. Because bone density develops in the course of adolescence?
A. Because it develops more rapidly during certain periods of adolescence.
Q. Did you ever attempt to locate and study the two systematic reviews that the Endocrine Society says they relied on in preparing these guidelines from 2017?
MS. EAGAN: Just to be clear, you're talking about has she gone back and looked at more detail at the two that are mentioned in this section, Commissioned Systematic Review on Page 3873; that's what you're asking?
MR. BROOKS: That's exactly what I mean.
Q. Have you attempted to locate -- determine whether those are published and locate them and review them?
A. Well, I may have reviewed them. I have not intentionally done that relative to this

paragraph in the last couple of weeks.
Q. Do you know whether you've ever read the systematic reviews referred to in this paragraph?
A. If I saw the reference or the exact paper, I might.
Q. But the Endocrine Society didn't give us a reference, so my question stands: Do you know whether you have ever read the systematic reviews referred to by the Endocrine Society in this paragraph?
A. Given only this paragraph to look at, I do not. But I've reviewed many, so.
Q. Are you familiar with an organization called the Cochrane Library?
A. I'm familiar with it.
Q. And are you aware of its reputation as a respected source of systematic reviews of medical evidence?
A. Cochrane reviews have been around for a long time, and they're a respected organization.
MR. BROOKS: Let me mark Ladinsky

Exhibit 11 a document with the Cochrane Library logo on it titled "Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women (Review)." The first author being Haupt.

(Whereupon, Ladinsky Exhibit 11 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) My first question will be, Dr. Ladinsky, whether you think you've ever seen this document before today?
A. I don't believe I've seen or reviewed this particular document.
Q. Is it consistent with your understanding that antiandrogen or estradiol are hormone therapies used in treatment of natal males who desire to pursue a feminine gender identity?
A. I am.
Q. And, indeed, those are cross-sex hormones in that application that your clinic sometimes prescribes; am I right?

A. That's correct.
Q. Does it surprise you that you have not previously seen this 2020 systematic review of cross-sex hormones prescribed in your clinic that was issued by a respected source of medical systematic reviews?
MS. EAGAN: Object to the form in your phrase couch -- excuse me. How you've couched this document. She said she's never reviewed this document. If you're going to ask her questions about the document and what it is, I would ask that we would be able to take a break so she can review it and she have time to familiarize herself with the document.
MR. BROOKS: Well, I'm not yet and I may not ask questions about the detailed contents.
Q. But given your early testimony about the reputation of the Cochrane Library and your testimony that part of your job is to stay current in the literature, let me ask a slightly different question.
Isn't a systematic review from the Cochrane Library of the use of antiandrogen or

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estradiol treatments in transitioning in transgender women a source of information that you would want to be aware of in the course of your professional duties?

MS. EAGAN: Object to the form.

A. Only if it were relevant and timely. Relevant with regard to the group of patients that I study and work with, not that I work with.

Q. (BY MR. BROOKS) Well, you've testified that these are cross-sex hormones that you use on minors, correct?

A. That's correct.

Q. And this study down in the left-hand corner of the first page shows a date of 2020, correct?

A. It does. But if we look at when the records that they analyzed were obtained was that well before 2020 in addition --

MS. EAGAN: I think it's best if you're going to ask her questions about the document, whether it's something she would be -- important to her, it's only fair to give her time the read the document. We can take a break for

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that or -- but I don't want her to answer questions without knowing what this document is.

MR. BROOKS: We won't take a break, and I'm not asking questions about the substance of the document.

Q. It's your understanding, Dr. Ladinsky, is it not, that a continued thorough systematic review is going to consider papers across the span of time up until the systematic review is performed?

MS. EAGAN: Object to the form.

A. Researched studies up to 19 December 2019.

Q. (BY MR. BROOKS) I didn't ask you a question about this document.

MR. BROOKS: Would you read the question?

MS. EAGAN: He's asking you about just in general. Listen to his question.

MR. BROOKS: Let me ask you to read the question back.

(Whereupon, a portion of the testimony was read by the court reporter.)

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A. I mean, to my recollection, Cochrane reviews focus more on type of studies that have been reviewed and analyzed, less of content.

Q. (BY MR. BROOKS) It's your understanding that Cochrane reviews, Cochrane systematic reviews are not applying GRADE criteria to evaluate the strength of evidence in medical fields?

A. I know they weight strength of evidence relative to study designs systematically. I'm not aware if they use the exact GRADE system or not.

Q. Are you familiar with antiandrogen that is referred to commonly as CTA? I'm not asking you a question about the document.

A. I'm not.

Q. All right. Would you agree that before prescribing antiandrogens or estradiol as a therapy for gender dysphoria, it would be important to have reliable information as to

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results including outcomes of feminization, sexual function, and reduction of gender dysphoria?

A. Best available evidence, sure.

Q. Well, before prescribing body-altering hormones, is it not your opinion that you would want to have reliable evidence on those topics?

A. I believe so.

Q. It's information that you want to the maximum extent it's available, correct?

A. Correct.

Q. Are you able to point to any randomized control study or what you consider to be a methodologically statistically reliable cohort study that, in your opinion, sufficiently establishes the efficacy and safety of hormonal treatments for males transitioning to female gender identities?

A. I think there are a compilation of studies that were taken together analyzed by consensus opinion as you see done in WPATH in the Endocrine Society's guidelines. There is, you know, solid evidence on that.

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Q. What do you consider to be the most statistically reliable cohort study relevant to establishing the efficacy and safety of hormonal treatments for male transitioning to female gender identities?

MS. EAGAN: You're asking here to identify one specific study?

MR. BROOKS: I am.

MS. EAGAN: Object to the form unless -- I mean --

MR. BROOKS: Counsel, I have been relaxed about it, but you're supposed to say objection and stick with that.

MS. EAGAN: Not in Alabama. You object to the form.

MR. BROOKS: Exactly. You object to the form, but I'm hearing a lot more than that.

MS. EAGAN: I don't think I said anything more than that. But, I mean, she can answer if she has an opinion on what particular study. I will say, you know, when you look at her expert disclosure, you really are going in areas that are not really what we are tendering her

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specifically for as an expert. If she has an opinion, she's welcome to talk about it. But when it comes to all these studies and all that --

MR. BROOKS: Counsel --

MS. EAGAN: -- our other experts will talk about that.

MR. BROOKS: Counsel, lectures, no. And she's offered views on safety and efficacy. And I'm asking questions about the foundation, and I am utterly within the zone.

MS. EAGAN: I'm allowing you to ask your question. I just want to make clear that there will be another expert that will address some of these studies and data in more detail than she as a clinician. But if she has an opinion, she certainly is welcome to offer that.

Q. (BY MR. BROOKS) Dr. Ladinsky, you offered opinions in courts previously that hormonal treatments were safe and efficacious. And my question for you is: What specific studies -- study or studies do you consider to provide the most statistically reliable evidence of the efficacy and safety of hormonal treatments

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for males transitioning to a female gender identity?

A. I think the body of studies coming out in the last two years, preliminary data from study in the Journal of Medicine. But it's a compilation of such tendered with expert scientific consensus and oversight that gives us as clinicians on the ground the information to not just treat our patients and see -- but what -- in addition, what to always be sure we're discussing with patients.

Q. Is it the case that as a clinician you primarily rely on what you refer to as consensus opinion as reflected in the WPATH and Endocrine Society Guidelines rather than attempting to form your own opinion based on the peer-reviewed literature as to what is or is not safe and efficacious?

A. We utilize all of it together in the context of cost, benefit for each patient in front of us.

Q. Correct. Then let's go back to the literature. You mentioned Chen's recent paper.

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Is there any other paper that you want to identify as providing what, in your opinion, is reliable evidence of the safety and efficacy of cross-sex hormonal treatments for males seeking to transition to a female gender identity?

A. Not at this time when it comes to specific details of specific studies.

Q. You testified preliminary injunction hearing that you were -- you were asked. I'll refer you to Page 125 of that testimony. It is 12.

You were asked about a statement from Sweden's National Board of Health. And what I want to ask you now is: What you said was, "I'm not imminently apprised of that." I'm going to ask you a little bit more about Sweden.

At the time of that testimony, were you aware of the policy statement put out by Sweden in February of 2022?

A. I was not.

Q. So the question on the stand was the first you had heard of that?

A. I believe so.

Q. Have you since then gone and reviewed at least the official English language summary put out by the Swedish health authority?

A. Not in immense detail.

Q. Have you read it?

A. I'm not sure we're referring to the same document. If you have the document, I'll be happy to look at it and tell you if I've seen it before.

MR. BROOKS: Let me mark this Ladinsky Exhibit 12 the document "Care of children and adolescents with gender dysphoria. Summary."

(Whereupon, Ladinsky Exhibit 12 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) My question at this point is simply whether you believe you've read this document before today?

A. I've skimmed it.

Q. How did you obtain it?

A. It's on the Internet. If it's the

same document.

Q. Have you made any efforts to obtain documents related to the systematic review of the literature relating to treatment of gender dysphoria in minors that was commissioned by the Swedish health authority?

A. No, I have not. I've simply skimmed what they have in the public domain.

MR. BROOKS: I want to mark as Ladinsky Exhibit 13 what is titled "Appendix 3. Characteristics of included studies: Extracted data." Dated 2022.

(Whereupon, Ladinsky Exhibit 13 was marked and copy of same is attached hereto.)

MR. BROOKS: I want to mark as Ladinsky Exhibit 14 a document titled "Appendix 2 Studies excluded due to high risk of bias." Also dated 2022.

(Whereupon, Ladinsky Exhibit 14 was

marked and copy of same is attached hereto.)

Q. (BY MS. EAGAN) Dr. Ladinsky, these documents are in the public domain and with modest exceptions are in English. Are these documents that you've obtained and reviewed before today?

A. Certainly not exhaustively. I do believe I've skimmed some of them.

Q. Exhibit 14 is the excluded studies taken.

A. Okay.

Q. Is this a document that you've reviewed before today?

A. No, sir.

Q. So you don't have any -- they're described as "excluded due to high risk of bias." Do you see that language?

A. I see that.

Q. Do you have an understanding of a formal or technical meaning of bias relevant to medical research literature?

A. I believe that these are studies

whose methodology is quite dissimilar from a randomized double-blind placebo-controlled study.

Q. Do you have an understanding of the technical meaning of bias when it comes to discussion of the results of research studies?

A. To a superficial extent.

Q. What is that extent?

A. Simply that there can be confounders. There can be elements influencing the results that may not have been controlled for in the same way they could have in an RCT, randomized controlled trial. It does not mean the results are insignificant or should be adopted or not adopted. It simply refers to study methodology and the ability to eliminate confounders.

Q. And aspects of methodology that create a high risk of bias, am I correct, can result in the results being unreliable or I should say unpredictive of results that would be obtained in other patients?

A. I don't agree with that. As a clinician I see that term as perhaps the study

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findings are less generalizable.
Q. Do you believe that you have previously reviewed the document that I've marked as Ladinsky Exhibit 13 which is a list of included studies?
A. I do not. I've not seen this. It's just extracted --
MS. EAGAN: I think the question was: Have you seen or recall seeing DX 13?
A. No.
MR. BROOKS: Let me mark as Ladinsky Exhibit 15 a document entitled "Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria." Dated October 2020.

(Whereupon, Ladinsky Exhibit 15 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) And Dr. Ladinsky, this document says in its opening paragraph, quote, "This document will help inform Dr. Hilary

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Cass' independent review into gender identity services for children and young people." And it goes on.
But is this a document that you have studied before today?
A. No, sir.
Q. Are you familiar with a report issued by Dr. Hilary Cass to the English health service in 2022?
A. I believe it's an interim report.
Q. It is titled "Interim report." Have you studied that document with some care?
A. Not studied it but I'm familiar with it.
Q. And given your desire to stay current in the scientific knowledge in your field, why have you not before today reviewed the analysis and conclusions of this evidence review prepared by the NICE organization in England?
MS. EAGAN: Object to the form.
A. I've read it but I'm not going to say I read every single page and every single word in deep deep detail. These are Dr. Cass' interim

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recommendations.
Q. (BY MR. BROOKS) I'm sorry. Let me be clear in my question because we're confusing documents.
Back to Exhibit 15, which is the evidence review, not the interim report. We talked earlier in the context of evidence-based medicine about the role of systematic reviews. And my question is: Given the testimony you have given about your desire to stay current and knowledgeable about the scientific knowledge in your field, why have you not studied the analysis and conclusions of this systematic review of puberty blockers as a treatment of gender dysphoria in children and adolescents?
MS. EAGAN: Object to the form.
A. This document that I'm looking at was never elevated to my attention in the form it is right here.
Q. (BY MR. BROOKS) Do you have any knowledge as to whether this particular systematic review has been cited by healthcare authorities in other European countries?

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A. I do not. I have no knowledge.
Q. Do you have any knowledge as to whether it's been cited by healthcare authorities in various states of the United States?
A. I do not.
Q. Do you have any knowledge as to whether this systematic review is the most comprehensive and detailed systematic review of the literature relating to use of puberty blockers in minors that have been performed to date?
A. I do not.
Q. As a clinician, it is important to you to have the best available knowledge with regard to the clinical effectiveness of treatment of children and adolescents with puberty blockers compared with treatment relying solely on psychological support, correct?
MS. EAGAN: Object to the form and the term "best available".
MR. BROOKS: Let's hear the question back.

(Whereupon, a portion of the

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testimony was read by the court reporter.)

MS. EAGAN: Object to the form.

A. I would think it's important to all clinicians, but I'm not sure really what you're asking.

Q. (BY MR. BROOKS) I'm asking: Don't you want to be aware of the latest information and best analysis with regard to the safety and efficacy of puberty blockers as a treatment for gender dysphoria in minors as compared to the alternative of psychological support and psychotherapy alone?

A. Like I said, I'm not sure what you're trying to ask.

Q. What part of my question is unclear to you?

A. The idea of comparing those two groups.

Q. Well, you testified earlier that in your own clinic you're able to significantly ameliorate distress by means of psychotherapy and

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support prior to administration of hormones, correct?

MS. EAGAN: Object to the form. Misstates previous testimony.

A. Only -- it's not that that's -- I mean --

THE WITNESS: Should I answer that?

MS. EAGAN: I mean --

MR. BROOKS: That's how it works. I will ask the court reporter to read the question.

(Whereupon, a portion of the testimony was read by the court reporter.)

A. Okay. So youth who are not currently receiving puberty blockers or hormones, okay, either because they're too young or not quite eligible for such are not simply set out with psychotherapy alone. These youth by and large have made a social transition and are living in their identity. They're not a homogeneous

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group of patients. Each one is unique and different. But for these youth with significant gender dysphoria in our space and having been referred to us, they're not a case-controlled group. They're -- those eligible for puberty blocking medication may receive it. Individual cases. Each one is looked at. Others may not yet be eligible or may be of an age that they're no longer eligible. However, they are living in their identity. Family, work is going on, therapy is going on. And they see down the line that they may become eligible for hormonal therapy. Those are taken together what can allay the dysphoria. Not a single intervention. So I guess where I had trouble with that one is that I don't see these two groups -- eligible for puberty blockers, you get them, you don't. Let me compare them. I don't see that as a safe or realistic description of the use for hormonal care.

Q. Well, let me ask, I guess, a simpler question.

A. Okay.

Q. Isn't it important to you as a

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clinician to know how the effectiveness for reducing gender dysphoria of puberty blockers or cross-sex hormones compares in outcomes to psychological support and psychotherapy alone without medical intervention?

A. I believe we have a wide body of research that helps us understand that. I don't believe that those two hypothetical groups would be eligible for a prospective randomized controlled trial to understand that.

Q. Nor did I ask you that.

A. Okay. Just making sure.

Q. What I asked you was: Don't you believe it's important to you as a clinician to have the best available information about the relative efficacy for relieving gender dysphoria in minors of hormonal interventions on the one hand and psychotherapeutic interventions without medical intervention on the other?

MS. EAGAN: Object to the form.

A. And I believe a wide body of research does discuss that.

Q. (BY MR. BROOKS) I didn't ask that.

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I asked whether it's important to you as a clinician to have the best available information on that question?
A. It's important to have the best available information on anything that pertains to my patients.
Q. And it would likewise be important to parents of a child facing medical choices for a gender dysphoric child to have that information?
MS. EAGAN: Object to the form.
A. It's important for parents to have all of the available information.
Q. (BY MR. BROOKS) And it's important for medical health policy-makers to have that information?
MS. EAGAN: Object to the form.
A. When you say policy-makers, do you mean governments, institutions, consensus bodies issuing recommendations?
Q. (BY MR. BROOKS) I mean any organization that is making recommendations or making decisions about reimbursement or making decisions about availability, making decisions

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about medical policy?
A. On a very general level, it would be relative to any proposed treatment or any proposed medical intervention.
Q. And likewise, I was asking about efficacy. It's important to you as a clinician to have the best available information about both short-term and long-term safety of hormonal interventions on the one hand and psychotherapeutic support and counseling without medical interventions on the other?
MS. EAGAN: Object to the form.
A. The former, absolutely. The latter, there's a wide body of evidence as well as clinical experience which shows us that that is not a population I would propose to study.
MR. BROOKS: Let me ask you to read back the question.

(Whereupon, a portion of the testimony was read by the court reporter.)

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MS. EAGAN: Object to the form.
Q. (BY MR. BROOKS) And you can try to answer the question.
A. I thought I just did.
Q. And I think you -- is it your testimony that you don't consider it important to have the best available information about short and long-term safety of psychotherapy and counseling support as a treatment for gender dysphoria in minors?
A. I think the relevant research and clinical experience to date informs us very well in those spheres. We are always evaluating ongoing work as it's done and comes in.
Q. Dr. Ladinsky, is it important to you as a clinician to have the best available evidence about the safety, both short and long term, of both hormonal interventions for gender dysphoria in minors and, on the other hand, treatments that rely on psychotherapy and counseling support, short and long term?
MS. EAGAN: Object to the term "available evidence" and the form. You can

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answer.
A. I don't -- I mean that's information that is very helpful, but I don't see a prospective study looking at those two groups as a safe ethical practical or doable entity. That would put people in harm's way.
MR. BROOKS: Let's take a break.

(Whereupon, a lunch recess was taken.)

Q. (BY MR. BROOKS) Let me ask you, Dr. Ladinsky, if you can find your expert report Tab 13 in the binder, and turn to Page 19 if you would.
And at the end of the only full paragraph on the page, it reads, "Suicidality is of particular concern for this population because the estimated lifetime prevalence of suicide attempts among transgender people is as high as 40 percent." Do you see that language?
A. I see it.
Q. And let me ask you first: Do you

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consider yourself an expert in suicide and suicidality?
A. I am not an expert in that area, no.
Q. And do you have any understanding as to whether the 40 percent number -- and I think in the Ivy complaint, actually you have a 45 percent number -- refers to actual attempts or intents or suicidal ideation?
A. I stated here, suicide attempts among transgender people as high as 40. And I agree with what's written right there.
Q. And --
A. Attempts.
Q. I just want to get clear on that before we went elsewhere.
I want to ask you some questions about suicide. Have you ever made any efforts to find research that reports information about actual completed suicide among gender dysphoric individuals, minors either before or after transition?
A. I've read a bit about that.
Q. And what studies are you aware of

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that provide information about actual suicide among that population either before or after transition?
A. I mean, again, as a clinician, sir, I'm not going to be encyclopedic on specific studies, who wrote them, when were they published, et cetera, but more in that generalized body of knowledge. So there are many that discuss this topic.
Q. There are many that discuss actual suicide rates is your testimony?
A. There are several that discuss suicide rates similar to what's quoted here.
Q. Are you -- what you've quoted here is not a suicidal rate. It's --
A. No.
Q. -- an attempt rate, correct?
A. It's a prevalence of suicide attempt. That's correct.
Q. While you're not an expert in suicide and suicidality, you understand that there is a very wide large difference between suicide attempts and actual completed suicide, correct?

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MS. EAGAN: Object to the form.
A. I'm not an expert. I think all of it -- all of it is inordinately concerning and front and center in care for this population.
Q. Do you know whether it is the case that the vast majority of suicidality among minors does not lead to suicide?
A. Your definition of suicidality is?
Q. It's a term I believe you used. Do you have a definition that you prefer to work with?
A. We consider it suicidality to -- it's a broad term to sort of encompass thoughts of actual intent to pursue, intent with a plan, failed action, completion. It's a very wide range group of thoughts or behaviors.
Q. Are you aware of any evidence of suicide by any prepubertal child believed to be the results of gender dysphoria?
MS. EAGAN: You said prepubertal?
MR. BROOKS: I did.
A. Am I aware of or have I read about; is that your question?

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Q. Are you aware of any evidence of actual completed suicide by any prepubertal child that's believed to be due to gender dysphoria?
A. I am not personally, but that doesn't mean it hasn't happened.
Q. All I can ask you about today is what you know.
A. Sure.
Q. You would agree with me, would you not, that evidence relating to actual completed suicide whether before -- among gender dysphoric minors whether before or after transition could be quite important for considerations of clinical decisions, informed consent?
A. Yes.
Q. Are you aware of any study that demonstrates that medical transition of any type reduces the rate of completed suicides among any gender dysphoric population whether adult or minor?
A. I cannot speak to specific studies, but I believe the body of literature helps us in showing that transgender people who are afforded

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the ability to live, present, you know, consistent with their identified gender will have less suicide attempts completion.

Q. And my question was not about suicide attempts. So let's -- I want to talk about suicide, people who die.

Do you believe -- have you ever read any study that concluded that medical transition of any type reduced the rate of suicide among gender dysphoric population?

A. As I've said, I'm not, you know, the researcher that knows every single study in its isolation. But I believe there's a body of evidence that helps us affirm that.

Q. When you refer to a body of evidence, what are you referring to?

A. Collections of data.

Q. What collections of data?

A. I mean --

Q. Dr. Ladinsky, if the answer is I don't know, then that's the answer. I want you to identify for me what you're referring to as a body of evidence.

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A. I cannot point to specific study or a specific compilation of studies.

Q. Would you agree that the long-term effects of hormones on suicide, completed suicide is at least as important to a meaningful evaluation of the beneficence of such procedures as are measures of short-term happiness?

A. That was a mouthful.

MR. BROOKS: She can read it back.

(Whereupon, a portion of the testimony was read by the court reporter.)

A. I'm not a medical ethicist, and I will not render an opinion on that.

Q. (BY MR. BROOKS) All right. Let me ask a slightly more general question. Would you agree that the long-term effects of hormones on health and mental health into the adult years are at least as important to the meaningful evaluation of the ethics of administering those treatments to children as are the short-term effects?

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Long-term effects --

A. Right.

Q. -- need to be considered at least as important as short-term effects; would you agree with that?

A. We're talking about long-term and short-term effects. I'm happy to do so with one caveat. Those treatments are never administered to children. But if we're talking about adolescents going forward, that's a little bit clearer.

Q. To be clear on the record, I accept your making it more precise.

A. Thank you. So I'm not going to make a value statement about care in adolescents versus quality of life in adulthood. It's critically important that we are well aware of -- and we discuss with families -- potential long-term effects of these medications on their young person in adulthood.

Q. That is you as a clinician. It's not appropriate for you to focus with the family, with the child just on short-term mental health

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and happiness?

A. Agree. It's a comprehensive discussion.

Q. And do you have any view as to whether data as to whether hormones increase or decrease death by suicide in the long term would be relevant to whether a doctor can ethically prescribe such medications to adolescents?

A. I don't believe I can answer that in a yes or no, you know, using the principles of ethics that our medical ethicists use because I'm not one. I do think the discussion of what is known about long-term effects must come into and is part and parcel of the discussions we have with families around the care we provide.

Q. You're a doctor who has obligations under medical ethical principles; am I correct?

A. That's correct.

Q. And yet you're unable to tell me whether, in your view, data about whether hormones increase or decrease death by suicide in the long term is relevant to the question of whether you can ethically prescribe those hormones to an

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adolescent?
MS. EAGAN: Object to the form.
A. It's extremely difficult to draw a linear relationship between one medication or one course of medical therapy in adolescents and suicide in adulthood because there's so many different factors and life trajectories that impact one to the other.
Q. (BY MR. BROOKS) Does your clinic maintain contact and records with your patients that enable you to know with confidence how many of those for whom your clinic has prescribed cross-sex hormones as adolescents or its young adults have subsequently committed suicide?
A. We do not have a formal mechanism around, you know, obtaining that data going forward in the same way as in my primary care pediatric clinic. We don't have a systematic way of tracking parameters of health and well-being once our patients graduate from our space and go on into college or adulthood. One would hope we would be apprised of a tragedy like that through families. Because we get to know our families

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very well, and we have fortunately never received that phone call.
MR. BROOKS: Let me mark as Ladinsky Exhibit 16 a paper entitled "Psychosocial Functioning in Transgender Youth after 2 Years of Hormone." By Diane Chen and many other authors. From 2023.

(Whereupon, Ladinsky Exhibit 16 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, am I correct that this is a paper that you referred to in testimony this morning?
A. I have reviewed this document, yes.
Q. And you referred to it specifically in testimony this morning, correct?
A. Uh-huh. As a study that gives us time zero going forward prospective.
Q. And is Diane Chen or these other coauthors respected researchers in your field to your knowledge?

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A. I do not know all of them. But those whose names I've seen, the answer is yes.
Q. What names stand out that you are able to direct us to?
A. Drs. Rosenthal, Hidalgo, Ehrensaft, Olson-Kennedy.
Q. Is Dr. Chen among those whose reputation you know?
A. Quite possibly. I just -- remember I'm not a researcher. I'm a clinician. I'm not --
Q. But this is a paper that you studied for some care after it came out?
A. I've read it. I don't know that I could quote you exact details of any given anything, but I'm happy to --
Q. Well, I couldn't either. But just a few details I want to ask you about.
A. Let's do it.
Q. Sticking with the first page where things are simplified a bit. Under results, it refers to a total of 315 transgender and nonbinary participants. That seems to be -- you understand

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that to be the study size?
A. Study population.
Q. Study population?
A. Correct.
Q. Thank you. And it says that they have a mean age of 16 when they were enrolled. Standard deviation of 1.9, right?
A. I would have to look at methods to find out if that 16 reflects when they were enrolled or when the evaluative analysis was done.
Q. Okay. It says with mean age of 16 were enrolled.
A. Perfect.
Q. But I don't know the math terms on that so I won't take time.
A. No worries.
Q. And the study covers -- if you look at conclusions or the title of the study, it covers two years following the beginning of hormone treatments for adolescents, correct?
A. I believe so.
Q. If you turn with me to Page 243, it tells us -- about 3 or 4 inches down in the first

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column in 243 -- that two participants died by suicide during the study, one after 6 months of follow-up and the after 12 months of follow-up. Do you see that?

A. Yes, I do.

Q. And so for one, that was 6 months after beginning hormonal treatment; and for the other, it was approximately a year after beginning hormonal treatment, correct?

A. That's correct. That's what it says.

Q. And that is -- across the span, that is of the study population of 315, two committed suicide within a year of beginning cross-sex hormonal treatments, right?

A. That's correct.

Q. And if you turn with me to Page 245 and Table 2, the authors identify death by suicide. There's two deaths by suicide as adverse events associated with this study, correct?

A. That's what they state in this chart. I would have to go back to see exactly how they -- what they -- what the conclusion criteria

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were for an adverse.

Q. The authors --

A. That's what they say.

Q. The authors label those suicides as adverse events in this study?

A. Absolutely.

Q. Are you aware of -- so that's 2 out of 315 in the course of a year. That's a rate of something more than one-half percent mortality in a year, agree? 2 is more than half a percent of 315?

A. The most. Okay. I'm not doing math in my head right now.

Q. You know what, I'm going to represent to you that 2 divided by 315 is about .6 percent?

A. Not even 1 percent, okay.

Q. Well you said not even 1 percent. But are you able to point me to any study or any compilation or any body of information anywhere that found that high a rate of death by suicide among gender dysphoric adolescents who had not received cross-sex hormones?

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A. I think my first question is this, and I don't know the answer.

Q. I ask the questions, but you can go ahead.

A. Where my brain is going to be able to answer your question is what is the prevalence of suicide in the general population if we took a group of people who are 16 plus or minus 1.9 years.

Q. That is because we don't have a control here, you can't attribute causation?

A. No, I did not say that.

Q. Wouldn't you say it?

A. No. I only -- all I said was in order to answer that question, I would love to know the answer to my first thought: What is the population prevalence relative to this group -- this age group of young adults currently in America.

Q. Without being an expert in suicide, you know, do you not, that the general adolescent population does not exhibit an annual suicide rate of half a percent?

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A. I don't know what the exact number is.

Q. But let me ask again whether you're aware of any study or summary or body of knowledge that found a rate of suicide as high as half a percent per year among gender dysphoric adolescents who had not been subjected to cross-sex hormones?

A. I cannot point you to a singular study. But my inference from my own clinical experiences, it would be higher. And given the youth I see in the hospital, I would imagine it would be higher.

Q. You would imagine that?

A. I would imagine that. I don't have an exact study to point you to.

Q. Dr. Ladinsky, would you not agree that in this paper, Dr. Chen and Olson-Kennedy and others report what is in fact a catastrophic suicide rate?

MS. EAGAN: Object to the form.

A. I would only say that they report that using that adjective if they stated that in

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the study. Can I look through and see if that's in their conclusion?
Q. They don't use that word.
A. Okay.
Q. I'm asking for your opinion.
A. Okay.
Q. Isn't this a stunningly high suicide rate, 2 out of 315 in just one year?
A. I would not call that catastrophic.
Q. All right. Do you believe that the rate of suicide that they experienced amongst their study population is unexpectedly high among a population receiving cross-sex hormones?
A. No, sir, I don't.
Q. Do you think that a reasonable parent considering whether to approve cross-sex hormones for their adolescent child would want to know that this recent study by Chen, et al., observed a completed suicide rate deaths of 2 out of 315 in just a year?
MS. EAGAN: Object to the form.
A. I've never had a parent ask for that figure as we discuss use of these medications for

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their own individual young person.
Q. (BY MR. BROOKS) And if they don't ask, you don't tell?
MS. EAGAN: Object to the form.
A. I don't think that's an appropriate statement to say what we do or don't do in counseling families relative to these medications.
Q. Let me re-ask my original question. Don't you believe that a parent considering whether or not to approve cross-sex hormones for their adolescent child would want to know that this recent and prominent study experienced an actual death rate of 2 out of 315 adolescents in just one year?
A. I can't speak for what any parent would or would not want to know.
Q. Are you a parent?
A. I am.
Q. Wouldn't you want to know that?
A. I would want to know -- and I'm kind of bringing with you the framework that many of the parents come to us with. They are aware of very high suicide rates or rates of suicidal

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ideation among transgender people who have not had the opportunity or even those who may have to live in accordance with their identity. Most parents are very aware of that. They also may have experienced it in their child. So would they want to know, is there data that suicide can still happen even while my child is receiving medication? I can't tell you if they would want to know that or not. But I'm saying it's -- I can't put myself in the place of any one parent. It's a very complex interplay in these rooms with each individual patient.
Q. When you read the Chen, et al., study just out this year, am I correct in assuming that you noticed the data about the two suicides?
A. I did.
Q. So you're aware of that?
A. That's for sure. I'm sorry. Yes, I am aware of that.
Q. You can say that's for sure.
A. No. It's more of an expression than a statement of empirical fact.
Q. Are you aware of any data from any

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source that reports an equally high rate of suicide per year among an untreated gender dysphoric population?
A. I am not aware of any specific data set.
MR. BROOKS: We'll mark as Ladinsky 17 an article by Dutch name Wiepjes, W-i-e-p-j-e-s, and others dated 2020. Titled "Trends in suicide death risk in transgender people: results from the Amsterdam Cohort of Gender Dysphoria study (1972 to 2017)."

(Whereupon, Ladinsky Exhibit 17 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, you cite at least one different paper by Wiepjes in your expert report, but I don't recall whether you cited this one. Is this a paper that you're familiar with?
A. I'm not.
Q. Are you familiar with the existence

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of a number of papers over the years coming out of the so-called Amsterdam cohort?
A. Peripherally.
Q. And looking at the authors here, you see Wiepjes, Steensma, and others?
A. Uh-huh.
Q. And do you have any knowledge as to the reputation of those researchers?
A. The final author. Steensma appears throughout the literature.
Q. If you look in the methods summary on the first page, it describes this as a chart study including all -- just on the very first page where it says methods.
"A chart study, including all 8,263 referrals to our clinic since 1972." Do you see that?
A. I do.
Q. Do you have an understanding of what a chart study is?
A. Retrospective chart review, yes, sir, I do.
Q. Can you describe briefly what a

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chart study is?
A. It's where researchers at time, a certain fixed point in time review backwards information simply from what is documented in the medical record looking at a certain population around a certain study metric.
Q. And these -- this team had perhaps due to the medical record structures of the Netherlands a very large study population, correct?
A. It's a good number.
Q. They claim that it's everybody who has been referred to their clinic since 1972, correct?
A. That's what they claim.
Q. And this is one of the world's preeminent gender clinics?
A. Certainly one of the earliest.
Q. Are you not willing to concede that to this day it's one of the world's preeminent gender clinic?
A. I think preeminent is a valuating term. So what one person may call preeminent,

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someone else may not.
Q. It is. But you're a professional in the field, and I want your opinion as to whether this is recognized as one of the preeminent gender clinics in the world?
A. It's a fair statement. Some would recognize it that way.
Q. How about you?
A. Honestly, I've never -- it's not something that I've said, oh, yeah, they're preeminent. I've just said, they were certainly one of the earliest and have phenomenal data and can be very instructive in how others do what they do.
Q. Let me take you to Page 489, the second column. And down to the very bottom crossing over into 490, I want to read a sentence to you. It says, quote, "In our cohort, both trans women and trans men show a three- to four-fold elevated risk of suicide compared with the population rate in the Netherlands and can therefore be considered a high risk group." Do you see that language?

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A. I do.
Q. And is that consistent with your general understanding of the -- strike that.
On Page 490 second column, these authors, including Dr. Steensma state in the first full paragraph, "An important finding was that the incidence for observed suicide deaths was almost equally distributed over the different stages of treatment." And if you go down another inch and a half is a sentence --
MS. EAGAN: Where are you reading?
THE WITNESS: Right there.
Q. (BY MR. BROOKS) And down an inch and a half is a sentence that reads, quote, "This indicates that vulnerability for suicide occurs similarly in the different stages of transition." Closed quote. Do you see that?
A. I do.
Q. If it's true that suicide occurs similarly both before and after transition, is that an important fact for clinical decisions about medical transition?
MS. EAGAN: Object to the form.

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A. That statement in isolation that risk of suicide for transgender people before, during, within, and after transition remains elevated. That's an important element to know. It underscores a longitudinal mental health that's provided along the way. I think it's hard to generalize any statement from this cohort study, though, because it involves 1972 to 2017 in The Netherlands where social norms and acceptance of transgender people may not have been the same as what it is today because there are many factors that impact suicide from marginalized populations such as trans people.

Q. Dr. Ladinsky, if it's true as these authors report that the incidence of observed completed suicide deaths was almost equally distributed across the different stages of treatment; that is, before and after hormonal interventions, surgeries, the works, is that potentially an important consideration in deciding the clinical appropriateness of prescribing cross-sex hormones for minors?

A. In this study the mean age was 28,

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so these are adults going forward. But if you want to -- do you want to rephrase that relative to minors?

Q. No. I'll let the question stand as it is.

A. Can you --

Q. Do you believe -- I'll restate it to save time. If it's the case as these authors report that the actual rate of completed suicide is closely similar before and after medical intervention for gender dysphoria, is that potentially an important consideration for you as the clinician in deciding when or whether it's appropriate to prescribe cross-sex hormones?

MS. EAGAN: Dr. Ladinsky, if you need to read this document that you've never read to understand the context of that statement, she certainly is entitled to do so before answering that question, so.

MR. BROOKS: I didn't ask a question about the document and I disagree.

MS. EAGAN: Well, you've asked her about a conclusion that is stated in the document

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wouldn't that be an important consideration. She certainly should understand the context of the statement.

Q. My question -- and I'm happy to just take the document away so it's not a question about the document.

A. Okay. These is median age of first visit 28 years.

Q. If it is true that the rate of completed suicide is closely similar before and after hormonal interventions in individuals suffering with gender dysphoria, isn't that, in your opinion, an important fact you need to consider as a clinician in deciding whether to prescribe cross-sex hormones to adolescents?

A. Can I presume that you're asking that as a theoretical?

Q. Yes.

A. Okay. That helps. If that were true -- and I am not positing it as true. I don't believe it to be true. But if it were true, it would be an important thing not just to know, but it would also help govern the robust mental health

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oversight that's already very robust but further discussions would be had relative to that.

MR. BROOKS: I'm going to mark as Ladinsky Exhibit 18. A title of -- an article entitled "A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones" from 2011 with authors including Asscheman, Gooren, and others.

(Whereupon, Ladinsky Exhibit 18 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, this is a -- you'll see up at the top another article coming out of Vrije University or VU Center. And let me ask whether you believe you've seen this article before today?

A. I have not seen this article before today, sir.

Q. Have you ever made any organized effort to find literature that addressed actual suicide among gender dysphoria individuals?

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A. I've read a good bit about it in the literature I read. But have I, you know, done a Google search putting those terms together, no.
Q. Isn't it important to you to know what the literature knows about actual suicide among gender dysphoric individuals?
A. It's important to know what we know. This is an area where there is -- numbers may be higher than we know.
Q. In the abstract of this paper under design, it says this is "a cohort study with the median follow-up of 18.5 years at a university gender clinic." Do you see that?
A. I see that.
Q. In terms of the information available in your field, that's a very long follow-up study, correct?
A. It's hard because we're not comparing apples to apples again. This is a cohort study with a median follow-up at 18.5 years that enrolled adults at 31.4 and 26.1 mean age respectively. It may yield important information, but 18.5 years isn't something that's -- isn't

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fully generalizable to the adolescent. We take this for what it's worth.
Q. My only question at this point is: Compared to what's available in the literature, an 18.5 year follow-up is one of the longest studies that you're aware of; am I correct?
A. I do not know comparatively. I think it's a good length of follow-up.
MS. EAGAN: I would like for her to have time to get herself familiar with this document.
MR. BROOKS: Well, let's see what I have to ask.
MS. EAGAN: At this point she --
MR. BROOKS: I understand.
MS. EAGAN: We don't know what this document is you're asking.
MR. BROOKS: Suicide.
MS. EAGAN: Before questioning about the document, I would like for the witness to have an opportunity to familiarize herself with the document.
Q. (BY MR. BROOKS) Let me ask you to

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turn to Page 638.
A. Okay.
Q. Where we are within the results section if you turn back. In the second column towards the bottom is a paragraph that begins, "External causes of death were increased almost eightfold due to suicide and illicit drug use. The suicide rate in males to female was increased sixfold." Do you see that?
A. I do.
Q. And if it's the case that the suicide rate among post-transition transsexuals is eightfold or sixfold depending on which number we look at, is that a number that you think that parents considering whether to authorize medical transition of their child would want to know?
A. I would not use data produced from this particular study in my counseling of families in Birmingham, Alabama, in 2023. These are adults when they transitioned. They also transitioned in the 90s and early 2000s at a time when there were very, very different forces impacting the world in which they lived. HIV, AIDS was still very real

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in The Netherlands at that time as you see here. And what I glean from this that I will continue to use and counsel with families is that transgender people, regardless of transition, remain at risk for discrimination, of marginalization. And we will always work with that in the population we care for.
Q. I'm sorry. Remain at risk for what?
A. Marginalization, discrimination, societal challenges. That's what you'll see through here.
Q. Do you think that you take away from this also advising families that after transition, transgender individuals remain at high risk for actual completed suicide?
A. I would not draw that conclusion from this document, but that is something we -- that is within the sphere of the counseling we provide, the oversight, the work that we do.
Q. That is your disclosure to the parents for purposes of informed consent tells them that according to the available data, transgender individuals remain at high risk of

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completed suicide after transition?
MS. EAGAN: Object to the form.
A. I would have to look and see if that is a line item on our extensive informed consent document. But it is within the anticipatory guidance and counseling that's had with families that most all appointments relative to the importance of mental health, of coping, et cetera.
Q. (BY MR. BROOKS) Do you have an opinion as to whether data about suicide rates among individuals who have undergone transition surgeries is something you should consider as you decide whether to recommend or whether to authorize transitioning hormones?
A. It's not part and parcel of a discussion because we're looking -- when we're talking about initiation of hormonal therapy and the criteria that goes into that, we're not extrapolating years and years and years into the future presuming and assuming that every patient will one day have gender-affirming surgery. That's a very individualized decision made by adults.

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Q. In counseling families and adolescents about transition options, isn't it, in fact, part of your job to envision and help them envision life and outcomes years and years and years in the future?
A. Those are discussions that are always had.
Q. Is it part of your job?
A. I wouldn't say it's a line item in anything, but these are discussions that are had with -- by pediatricians in all contexts of the work that we do, not just gender health.
Q. To the extent that you as a gender specialist counsel parents and adolescents about transition, about medical transition, don't you consider that you have an ethical obligation to help them foresee outcomes and life years and years and years into the future?
A. I don't think anyone has a crystal ball. Your pediatrician doesn't foresee your children's life in the future but certainly helps and guides with medical decision-making around current health, sustained health, and health going forward. We do so to optimize the future.

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Q. Do you believe that as a doctor participating and advising parents and adolescents about medical transitions that you have an ethical obligation to help them think about not just the short term but about how this will affect their life and mental health years and years and years into the future?
A. I'm not sure I would say we have an ethical obligation to predict their health years and years and years into the future because we don't. No one does. But we certainly can talk about how to optimize that.
MR. BROOKS: Let me mark as Exhibit 19 a paper entitled "Suicide by Clinic-Referred Transgender Adolescents in the United Kingdom" by Michael Biggs dated 2022.

(Whereupon, Ladinsky Exhibit 19 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, are

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you familiar with the clinic that's referred to in some cases as the Gender Identity Development Services or GDIS or the Tavistock Clinic in England?
A. I'm well aware of it, yes.
Q. And I'll represent that this is a study of actual suicide rates based on extensive data from the Tavistock Clinic. My question right now simply is: Do you believe that you have seen this paper before today?
A. I don't.
Q. Would it be consistent with the understanding that the Tavistock Clinic has over the years served a large number of adolescents and would have a large dataset?
A. It would certainly have the largest dataset in the UK.
Q. And if a study of suicide among those referred to the Tavistock Clinic was published in 2022 and you had earlier testified about the various listservs and other things you rely on to bring relevant literature to your understanding, do you have an understanding how it

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could be that until now you're unaware of this paper from just last year about suicide at the Tavistock Clinic?

MS. EAGAN: Dr. Ladinsky, I would ask that you actually take the time to review the paper before you begin answering questions as to the paper's contents.

MR. BROOKS: And I haven't asked any questions about the paper's contents.

MS. EAGAN: Well, you have. That's what you're implying.

MR. BROOKS: I have not asked questions about the paper's contents nor do I intend to.

MS. EAGAN: Well, she still can review it.

MR. BROOKS: If you want to go off the clock since I'm not asking questions about it, we can go off the clock. But she cannot take my clock time reading a paper I'm not asking her questions about.

MS. EAGAN: That's fine. We can go off the clock. But I think before you're asking

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questions as to why she wasn't aware of this paper, she's certainly entitled to understand the contents of the paper and the context.

MR. BROOKS: Off we go.

(Whereupon, a brief recess was taken.)

Q. (BY MR. BROOKS) Have you heard or read the catchphrase "Would you rather have a living daughter or a dead son"?

A. I've heard that said.

Q. Or vice versa as the case may be. And are you aware that that catchphrase circulates on social media to a considerable extent?

A. I'm not.

Q. You're not?

A. I'm not a social media person.

Q. Me neither. And do you believe that you or your colleagues ever use that phrase in counseling parents or adolescents?

A. I do not and I have not heard it said in my clinic space when counseling parents.

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Q. And as you sit here today, you can't point to any specific data or paper that shows that hormonal intervention reduces actual rates of death by suicide among gender dysphoric adolescents, correct?

A. This one helps to assuage that concern.

Q. And you refer to?

A. The conclusion, "The proportion of individual patients who died by suicide was 0.03 percent, which is orders of magnitude smaller than the proportion of transgender adolescents who report attempting suicide when surveyed. The fact that deaths were so rare should provide some reassurance to transgender youth and their families."

Additionally, two of the patients who committed suicide known to the Tavistock Clinic included here were patients on the waiting list. That's important. They did not have the opportunity to get gender-affirming care or to even be considered eligible for some. Hope can save lives.

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Q. Dr. Ladinsky, are you aware of -- I won't take time to ask you what else you found. I wouldn't have pulled that out if that was all you found.

Are you aware of any data that shows that administration of cross-sex hormones or puberty blockers for adolescents or children reduces the actual rate of death by suicide?

A. I cannot refer you immediately in this instance.

Q. And absent that data, it's not scientifically supported to refer to those treatments as lifesaving, is it?

MS. EAGAN: Object to the form.

A. I don't think that's a fair statement at all. It does not describe what's in the literature. It's kind of an editorial comment that is not like an impaired statement.

Q. (BY MR. BROOKS) Well, you yourself have referred to those treatments as lifesaving, have you not?

A. If I have referred to them in any of these documents, then I have.

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Q. Putting aside documents created for litigation, you have from time to time referred to those treatments as lifesaving, have you not?
A. I'm not aware of that.
Q. Okay.
A. If you have evidence to that from a presentation I've made, then I guess I did. But in this moment, I don't recall it.
Q. In your opinion in counseling a parent given what we know and what we don't know, it would not be ethical to use that phrase, "Would you rather have a living daughter or a dead son," would it?
A. That is not a phrase I use in the counseling I provide.
Q. And you consider it to be unethical to say that to a parent, don't you?
A. I could not make a value judgment on it.
Q. Why not?
A. Because it's not appropriate.
Q. You as a doctor don't have to make value judgments as you counsel parents?

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A. Of course I make value judgments.
Q. Ethical judgments?
A. Ethical judgments within structure around framework. But to ask me if a certain idiomatic phrase is ethically just or not is not something I could answer. Most importantly it's not a phrase I use.
Q. Why not?
A. It's -- I mean, it's not the way that I talk or think, if that makes sense. When I emphasize -- when we talk about counseling families is data that reinforces the positive mental health impacts of transgender people being allowed to live in ways that are most aligned with their gender identity at each stage.
Q. Have you ever had a parent ask you, in essence, whether that's the choice they face, having a live daughter or a dead son?
A. I have not.
MS. EAGAN: Can we take like a five-minute bathroom break?
MR. BROOKS: Yes.

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(Whereupon, a brief recess was taken.)

Q. (BY MR. BROOKS) Let me ask you to find Exhibit 5, your expert report, which is in a binder. Turn to Page 29 if you would. In the middle of the page is a short paragraph that reads, "Dr. Hurz's suggestion that 'alteration of normal adolescent brain maturation' may be another 'possible side effect' of puberty blockers is not accurate. I have not seen this in my practice and science does not support this statement." Do you see that?
A. I do.
Q. And you cite a single paper in reference to your statement about science by Dr. Staphorsius, correct?
A. Correct.
Q. When you say "I have not seen this in my practice," let me ask whether in your practice you systematically make any tests of cognitive capability of your patients before and after treatment?

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A. No, sir. That is not part and parcel of standards of care in what we do. I assume you're implying neuropsychological evaluative examinations?
Q. Yes.
A. Okay.
Q. So when you say "I have not seen this in my practice," all you mean is that you haven't seen any effect on brain maturation that was dramatic enough for you just to notice it in ordinary interactions with the child?
A. More importantly, parents noticing elements of cognitive decline, academic decline that, you know, was --
Q. Well, your understanding as a pediatrician is that adolescence is -- healthy adolescence is a period of positive development and mental capability, correct?
A. In a general sense, yes.
Q. And you say "science does not support the statement." Did you have anything in mind in addition to the Staphorsius paper that you referenced?

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A. This is -- this paper is referenced because it directly addresses this from a neuropsychological perspective using what they identify as validated -- validated evaluations, executive functioning.

MR. BROOKS: Let me mark as Ladinsky Exhibit 20 an editorial by de Vries and Hannema from The New England Journal of Medicine dated 2023 entitled "Growing Evidence and Remaining Questions in Adolescent Transgender Care."

(Whereupon, Ladinsky Exhibit 20 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) And I believe you've testified earlier that de Vries is a researcher of strong reputation; am I correct?

A. That's fair.

Q. And this paper is -- this editorial, I should say. This is not a research paper. But The New England Journal of Medicine in which it was published is an extremely prestigious medical

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journal; am I correct?

A. It is.

Q. One of the premier journals in the world?

A. I believe that's fair.

Q. And on the next -- on the second page, 276, Column 2, writing in 2023, de Vries states -- and I'm 3 inches from the bottom. A paragraph that begins, quote, "Finally, benefits of early medical intervention, including puberty suppression, need to be weighed against possible adverse effects. For example, with regard to bone and brain development and fertility." Closed quote. Do you see that?

A. I do.

Q. Now, writing in 2023, Dr. de Vries thought that possible adverse effects of medical intervention in gender dysphoric youth and children were adverse effects on brain development. Do you agree that that's what's accurately described in what Dr. de Vries says?

A. I'm sorry. I'm going to have to ask you to repeat that because I was finishing reading

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that paragraph.

Q. Writing in 2023, Dr. de Vries listed as among possible adverse effects from medical intervention in children and adolescents negative impact on brain development, correct?

A. I believe Dr. de Vries posed this here as a question, not as a statement of fact.

Q. And do you disagree or agree with Dr. de Vries that as of 2023, it is an open question whether medical interventions in minors affect brain development in an adverse manner?

A. In her editorial or opinion commentary on the Chen article, her job is to do what physicians do. We work hard to elevate potential research questions. Dr. de Vries does state in that same paragraph, right, "that adolescents' educational achievements are as expected given their pretreatment status, which is reassuring." In other words, we do not have evidence of this. But as a research question, Dr. de Vries seems to find it merits asking.

Q. Well, indeed, Dr. de Vries says it merits weighing against possible benefits of

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medical intervention, does she not?

A. She does say that, and I take that to mean again she is probing. Because in her last paragraph, she continues that, Despite uncertainties that call for further study, current information shows that mental health improves with gender-affirming hormone, GAH, whereas withholding treatment may lead to, da, da, da, adversely affect psychological functioning.

Q. And mental health is a different question from brain development, do you agree?

A. She raises them as different questions, however, they are not inextricable.

Q. Endocrine Society is Tab 37. Let me ask you to turn to Ladinsky Exhibit 8, which is Tab 37 in the binder I gave you. And if you would turn to Page 3882. And under side effects in Column 1, the Endocrine Society, Guidelines, state that, "The primary risks of pubertal suppression in GD/gender incongruent adolescents may include" and she -- and then they list a number of things. One of which is, quote, "unknown effects on brain development," period, closed quote. Do you see

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that?
A. I see that.
Q. And I think you've testified you're not a neurologist, and you haven't done research in this area. Do you agree or disagree with the Endocrine Society Guidelines when they state that the effect of pubertal suppression on brain development in adolescents is unknown?
A. That is what they state right there. We must take some comfort in generalizing from the extended longitudinal data on young people treated with the same medication for central precocious puberty who are well into adulthood, and it does not show a decrement in cognitive development.
Q. Are you aware of studies of the effect of pubertal suppression or central precocious puberty that specifically measured cognitive development?
A. I am not aware of studies that may have measured cognitive development with neuropsychological tests.
Q. All right.
A. It doesn't mean they don't exist.

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Q. Let me ask you to turn to Page 3883, the next page there. And at the top of the first column, the first full paragraph reads, "Limited data are available regarding the effects of GnRH analogs." That's puberty blockers, correct?
A. Correct.
Q. "On brain development. A single cross-sectional study demonstrated no compromise of executive function."
A. Right.
Q. "But animal data suggest there may be effect of GnRH analogs on cognitive function." Closed quote. Do you see that?
A. I see that.
Q. And do you yourself have any knowledge concerning what animal data may -- does or does not show about the effect of blocking puberty on cognitive function?
A. I have no knowledge of this.
Q. Do you consider information from animal data to be at all relevant to reasonable inferences about effect on humans?
A. Less so when there is available data on humans, especially humans that are relevant to the population for which I work.

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Q. Now, the Endocrine Society Guidelines that are focused -- the committee that is focused specifically on puberty blockers and cross-sex hormones chose to warn here that animal data suggests that puberty blockers may have an effect on cognitive function. Do you consider that this committee or you have a more informed view on that question?
MS. EAGAN: Object to the form as to the term "warn".
A. I'm not sure what you're asking. Can you help me with that?
Q. (BY MR. BROOKS) I can ask it again. The Endocrine Society committee that prepares the guidelines state in the text that I read that animal data suggest there may be an effect of puberty blockers on the development of cognitive function, correct?
A. Relative to animal data, that's what they say right here, yes.
Q. And presumably, it's fair to say that they would not have included that information unless they thought it was at least potentially relevant to humans, correct?
A. I can not infer why they chose to include it or not. I do -- what my read as a frontline physician is this sentence is a testament to their robustness. They're inordinately thorough. They're not telling us what to do or not with this.
Q. Certainly you have no basis to disagree with the statement of the committee that animal data suggest that there may be an effect of puberty blockers on cognitive function, do you?
A. If that's what they state. I have no knowledge of it or knowledge to negate it.
MR. BROOKS: Let me mark as Exhibit 21 a paper entitled "Consensus Parameter: Research Methodologies to Evaluate Neurodevelopmental Effects of Pubertal Suppression in Transgender Youth" from 2020. Lead author is Diane Chen.

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(Whereupon, Ladinsky Exhibit 21 was

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marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, you understand Diane Chen to be one of the lead investigators in the ongoing prospective study that's reported on by the Chen paper that we looked at previously, correct?

A. I would assume so given her position at Lurie which is one of the forecenters.

Q. Which is one of the?

A. One of the forecenters involved in this prospective data collection.

Q. And here from three years earlier, 2020, is a paper specifically directed at research methodologies for evaluating the effect of puberty suppression on neurodevelopment or brain development. And my first question for you is: Have you seen this paper before?

A. I have not, sir.

Q. Are you familiar with something called a Delphi consensus procedure?

A. Not in detail but I'm familiar with

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its existence and what it is around obtaining expert consensus when asking a question in a scientific or a systematic way.

Q. Okay. Is it consistent with your understanding or is it outside your expertise that the adolescent period is associated with profound neurodevelopment including increase in capabilities for distraction and logical thinking?

A. That is outside my area of expertise to comment on it any quantitative way.

Q. Okay. And is it consistent with your understanding as a doctor or outside your expertise to say that several neurodevelopmental processes occur during adolescence including myelin development and changes in neural connectivity?

A. I think we're talking about -- I'm not -- not being a neurologist or neuroscientist, I could not give you, for example, the functional MRI components of which pathways are being pruned and fine-tuned.

Q. Well, then let me ask a more behavioral question. Is it consistent with your

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understanding or outside your expertise to say that the puberty process in humans has been linked to developmental changes in social and emotional processing as well as emotional control?

A. That's a generalization that, again, a two-part generalization that I don't have the capability -- I'm not a neuroscientist or neurologist to give you quantitative backing for either part of those.

Q. Okay. I always tell my witnesses, I don't know, is the quickest way out of some topics.

Let me take you however to Page 254.

MS. EAGAN: We can go off the record, but I would like for her to have a chance to review this report.

MR. BROOKS: I'll take her to the particular language, and then she can see what she wants to review around that.

MS. EAGAN: Okay.

Q. (BY MR. BROOKS) In 254, Column 1, these authors state -- and this is not a research paper. They are not reporting on data?

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A. Right.

Q. They state under discussion in the second sentence, I believe, 254.

A. Okay.

Q. 254 under discussion, second sentence reads, quote, "puberty is a major developmental process and the full consequences, (both beneficial and adverse) of suppressing endogenous puberty are not yet understood." Closed quote.

So my question for you -- and, again, this is -- there's no date reported in this paper. It's not a study. Do you agree or disagree with these authors when they state that "the full consequences of suppressing endogenous puberty are not yet understood?"

A. That's a statement that they make and have convened sort of a consensus -- group of experts to work on how to best evaluate that.

Q. And do you agree or disagree or is it outside your expertise to say the full consequences of suppressing endogenous puberty are not yet understood?

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A. Outside of my expertise to know how quantitatively, qualitatively, that's a fair statement.
Q. Let me ask you to turn to Page 249.
A. Okay.
Q. And the second column -- this isn't even a statement by the author. It's a question by the author. 249 second column. Towards the top it says, first full paragraph, "We employed a two-round Delphi procedure to obtain expert consensus regarding the most efficacious research design elements to address the following research question: What, if any, real-world impact does pubertal suppression have on transgender children's cognitive and neural development?" Closed quote. Do you see that?
A. I do.
Q. And do you agree that learning the answer to that question could have important clinical implications?
A. I think it's a research question that merits asking.
Q. Do you agree or disagree that

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knowing the real-world impact of pubertal suppression on cognitive and neural development could have important clinical implications?
A. In theory, it could.
Q. And the answer to that question could be important to you as a clinician, to parents, and to health policymakers, correct?
MS. EAGAN: Object to the form.
A. I think the results of a multi-center methodologic study, should it be undertaken, could have clinical ramifications, but that would depend completely upon the methodology, the possible confounders, the length of time. And just as they say there may be a larger database if more was available that the cohort could be compared to. In other words, validating the comparison groups. I would be interested also in youth who received the same medication at the same physiologic stage for central precocious puberty.
Q. So far as you know since this article was published in 2020 in the Transgender Health Journal, no researchers have undertaken the type of careful study that's described -- that

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you've just described to attempt to measure the real-world impact, if any, of pubertal suppression on children's cognitive and neural development?
A. I do not know.
Q. Let me ask you to turn to 248.
A. They do say here, the real -- it's on the record. "The real world clinical care considerations may well be undeveloped in the proposed research design."
MS. EAGAN: I don't think there is a question on the table right now.
THE WITNESS: I was just finishing up.
Q. (BY MR. BROOKS) I'll take your attention to Page 248.
A. Yes, sir.
MS. EAGAN: Dr. Ladinsky, if you need more time -- if you need any more time to review this document more robustly, we can go off the record and you can review it if you need to.
THE WITNESS: Well, if I'm going to be asked about the content of 248, which is probably the intro.

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Q. (BY MR. BROOKS) Again, I'm going ask you a question rather than a content question. Towards the bottom of 248 about an inch up is a sentence that begins animal studies.
A. Okay.
Q. 2 inches up.
A. I see it.
Q. It reads, "Animal studies demonstrate pubertal hormones exert broad neural influence, including effects on neurogenesis, differentiation, apoptosis, dendritic branching, spine density, and regional gray and white matter volumes," period. I'm afraid to ask whether I read that correctly?
A. You did pretty well.
Q. So Chen and these many authors also mention animal studies, as would you agree, suggestive or as flagging questions that need to be investigated?
A. I don't read this as suggestive. I read this as simply making a statement relative to findings on rodents and monkeys and projecting.
Q. In fact, medical research often

Page 202

begins by studying the effects of procedures or pharmaceuticals on rodents or monkeys before moving on to humans, correct?

A. It can definitely.

Q. Indeed, ethical principles often require that experiments be done on animals before they're done on humans, correct?

A. Completely depends on the nature of what's being studied.

Q. Let me ask you to turn to Page 253. Talk a little bit more about rodents. Column 2, 3 inches down. Says, quote, "studies in rodents show ovarian hormones, acting during puberty, program cognitive flexibility by exerting long-lasting effects on excitatory-inhibitory balance in the prefrontal cortex." Period. Do you see that?

A. I do.

Q. Do you have any reason to agree with that or is it simply outside your expertise that rodents studies have shown that ovarian hormones can have long-lasting effects in brain development?

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A. It is outside my area of expertise to comment on this finding and any semblance of generalized ability to higher-order animals and humans.

Q. You would agree, however, would you not, that a scientist who is faced with animal studies that report long-lasting effects, to use the phrase from the paper, of pubertal hormones on animal brain development should conclude at least that there is some possibility that pubertal hormones may also have broad influence on brain development in humans?

A. I don't agree with that statement. I don't know. I don't have the knowledge base to understand how the effect of pubertal hormones on brains; ergo, observed behavior in rodents are generalizable to that same impact in people or even primates with their higher-order brain functioning that takes into account so many environmental messages.

Q. Does data -- and I admit I'm curious as to what kind of intelligence test you would give to a rat, but that's another question.

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Before I showed you this Chen, et al., 2020 article, were you aware of references in literature relating to gender dysphoria and treatment for gender dysphoria to animal research and its potential in patients relating to brain development?

A. No, not in that way.

Q. And having seen these references in the Endocrine Society Guidelines and in the Chen, et al., paper, does that cause you as a clinician to want to know the answer to the question of whether puberty blockers in humans have long-lasting effects on a child's brain development?

A. You're asking from what I'm seeing here about findings relative to animals?

Q. Correct. And my question is: What you've seen just today -- and that's why I ask you before. You didn't know that before. From what you've seen today, does that make you as a clinician want to know the answer to the question of whether puberty blockers administered during the time of endogenous puberty have long-lasting

Page 205

effects on the neural development of that child?

A. I appreciate and have an eye to ongoing research. Does what I've read here about rodents concern me greatly, just the animal related information? For me personally as a frontline provider, it does not.

Q. Turn to Page 252 if you would. In the first column on 252, inch and a half from the bottom, the sentence begins, quote, "The effects of pubertal suppression." I'll give you a moment to find it.

A. Got it.

Q. "The effects of pubertal suppression may not appear for several years. Any GnRHa-related difference in brain structure is likely to be observed over the long term, rather than immediately." End of quote. Do you see that?

A. I do.

Q. And so Dr. Chen, the lead investigator in the currently ongoing NIH-funded prospective study, writes here that effects of puberty suppression on brain structure is, quote,

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"likely to be observed over the long term, rather than immediately." Closed quote. And my question for you is given that you're not a neurologist: Do you agree, disagree, or consider it beyond your expertise to comment on Dr. Chen's statement there?

A. So this one sentence, Dr. Chen's conjecture that the effects of pubertal suppression may not appear for several years. That?

Q. Yes.

A. Does it -- what was the question?

Q. My question is: Do you agree, disagree, or consider it outside your expertise to comment on that statement by Dr. Chen?

A. The latter. It's outside my expertise to comment on. Here it's really posed -- I see it posed as a research question, and I look forward to any data.

Q. Let me ask you to turn to Page 255. And in the first column almost halfway down the page, sentence begins, "Yet evidence suggests." Not quite halfway down the page.

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A. I'll get there.

MS. EAGAN: Take your time and read through the section.

A. I'm bringing the previous page's context into what you asked me to look at if it's okay.

Q. (BY MR. BROOKS) Of course it is.

A. Thanks.

Okay. I have a better context now. Thank you, sir.

Q. Okay. Back in the middle of the first column of 255.

A. Okay.

Q. There is statement that says, quote, "evidence suggests an overoccurrence of neurodiversity characteristics (especially related to autism) among gender-referred youth." It continues, "The neurodevelopmental impacts of pubertal suppression on neurodiverse, gender-diverse youth might well be different than in neurotypical gender-diverse youth, given variations in neurodevelopmental trajectories observed across neurodevelopmental conditions."

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Period. Closed quote.

Is it consistent with your own clinical observation that young people with neurodiversity characteristics, including autism, are disproportionally represented than those referred to your clinic as compared to the general population?

A. I think it is consistent subjectively with our experience.

Q. And before reading this, have you given any consideration to the question of whether the effect of puberty blockers on those types of young people might be different than it is on, I'll say, a clinically normal --

A. Neurotypical.

Q. Neurotypical youth?

A. Well, in fact, I was looking for a paragraph that addressed that and was grateful to find it.

Q. Okay. That is -- this is a question you have given some thought to in your professional work?

A. I think we all have but not in a

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negative way.

Q. Well, I take it that simply finding out the answer to the question of what impact it may have is not a negative or a positive question, correct?

A. I haven't even gone that far. I was just -- as this consensus article is looking at how to study the trajectory of neurodevelopment in patients who receive puberty blockers. It's to me important that it takes into account those with neurodiverse processing. Methodologically how will you make sure that any evaluation, to answer the question, is talking about takes the breadth and depth of the youth we see into account.

Q. And so far as you know, when it comes to the effect of puberty blockers on neurodevelopment, nobody has yet attempted any study to determine how, if at all, those effects differ on neuro atypical adolescence versus neuro typical adolescence?

A. Not that I'm aware of. It doesn't mean it doesn't exist.

Q. I know that I've looked enough

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that --
A. Yeah.
Q. -- I know it doesn't exist.
MR. BROOKS: I'm going to mark as Ladinsky Exhibit 22 a document entitled "The Cass Review, interim report" February 2022. This is in your binder behind Tab 55.

(Whereupon, Ladinsky Exhibit 22 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) And Dr. Ladinsky, I believe you testified earlier that sometime after this interim report was issued that you read it?
A. I have. I've reviewed it.
Q. And --
A. I can't quote intimate detail, though.
Q. I understand.
A. It's pretty long.
Q. It's pretty long. Do you have any knowledge as to the reputation of Dr. Hilary Cass?

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A. Not in detail. I believe that she's a retired psychologist, if that's correct, who had considerable experience in the GIDS.
Q. That's not correct.
A. Okay.
Q. She's a pediatrician. Whether she's retired or not, I couldn't say. She obviously had some time.
A. I believe she's retired.
Q. Is this a document that you have discussed with colleagues in your clinic?
A. It is not.
Q. Are you aware that this document has been cited with respect to health authorities in multiple countries?
A. I'm not aware of that.
Q. When you read the document, was it generally your opinion that it raised legitimate questions and concerns or did you think it was scientifically unreliable?
A. That's a tall ask because I believe more importantly the focus of Dr. Cass' immensely robust work is with an eye to evaluating capacity,

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competence capability to decentralize this care given by multi-disciplinary teams but with an eye to the need to do so in more than one location throughout the Kingdom looking towards Sweden. And so she took into account and continues to, the input from many, many, many providers in Britain's NHS at many levels.
Q. Let me ask you to -- let me ask you to turn to Page 38 of this document.
A. Okay.
Q. And there under -- this document is easy to refer to. It has these nice numbered paragraphs. Call your attention to 3.32.
A. Uh-huh.
Q. Where Dr. Cass writes, quote, "A closely linked concern is the unknown impacts on development, maturation, and cognition if a child or young person is not exposed to the physical, psychological, physiological, neurochemical and sexual changes that accompany adolescent hormone surges." Do you see that language?
A. I do.
Q. And do you agree that up to the

Page 213

present, the impacts of blocking, preventing puberty at its natural or endogenous time on development of maturation and cognition of that child is unknown?
MS. EAGAN: I'm sorry. Read back that question. I was reading the document and I missed the question.

(Whereupon, a portion of the testimony was read by the court reporter.)

A. I believe it's what level you're asking the question on. You know, myelination, dendrites, pruning on a very very physiologic level or robust development in how that individual's interacting in accordance with age-related expectations, meaning biological or sociologic. Is it unanswered?
Q. (BY MR. BROOKS) If I -- and indeed, the paragraph here speaks broadly to development and maturation, so let me narrow the question.
Do you agree that the impact of

Page 214

puberty blockers on the child's developmental cognition is up to the present unknown?
A. I don't know. It's beyond my expertise to answer that because it can be answered on different levels, as I said, by different specialists.
Q. Okay. Toward the bottom of that section, that column. Dr. Cass writes, "If pubertal sex hormones are essential to these brain maturation processes, this raises a secondary question of whether there is a critical time window for the processes to take place, or whether catch-up is possible when estrogen or testosterone is introduced later." Closed quote.
And my question for you is: Are you aware of any study that addresses the question of whether any negative impact on brain maturation due to puberty blockade can be made up if a child is later exposed to either endogenous or cross-sex hormones?
A. I am not aware if that has been systematically studied in the way you ask it.
Q. And in any context, are you aware of

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development processes -- strike that.
Dr. Cass refers to a critical time window. And let me ask whether in any context as a doctor you're aware of developmental processes that have to happen at a particular time in the sequence of a child's development or they cannot happen properly?
A. In a general sense in pediatrics, yes. Thinking of visual input during an infant's first six months kind of thing.
Q. That is if they don't get the appropriate visual input, there are certain neurodevelopmental things that don't add up?
A. They may have some visual impairment.
Q. Okay. But visual impairment has to do with nerves, right?
A. Well, that's -- when you talk about a critical window of development, there are some anatomic structures. There are some areas in the developing person that that has applicability.
Q. All right.
MR. BROOKS: I'm going to mark as

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Ladinsky 23 a paper entitled "Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria" by Staphorsius and others dated 2015.

(Whereupon, Ladinsky Exhibit 23 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, this is the paper that you cited in your expert report in connection with cognitive development; am I correct?
A. It's correct, sir.
Q. And you believe that you studied it with some care and are reasonably familiar with its contents?
A. Reasonably familiar.
Q. And would you agree with me that when it comes to impact of puberty suppression on executive functioning, to use the term that they use, that the results reported in the Staphorsius and Cohen-Kettenis paper are mixed?

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A. There are some sentences that might lead you to believe that. However, I'm not sure I completely agree.
Q. Well, needless to say, we'll look at it in more detail.
A. Okay.
Q. Just for context, this is dated 2015. It is again out of the Vrije University research clinic in Amsterdam, correct?
A. That's correct.
Q. And we saw earlier that in 2023, Dr. de Vries, in that clinic, stated that one possible effect of puberty blockers could be adverse effects on brain development, but I won't ask you about that again.
Let's look at what Staphorsius says about that. Now, the methodology here was to use the so-called Tower of London test. Can you -- do you have any understanding of how that is used to measure cognitive development?
A. It actually to my knowledge -- and remember I'm not a neuropsychologist or a neuroscientist, but this is a test that can be

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done on a computer. And it looks at, to an extent, visual spatial but more importantly what they're looking at is a part of the brain on the executive function which has to do with planning and organizing. I don't believe that test elucidates somebody's cognitive development which is more like age appropriate or even IQs.

Q. So, and I used the wrong term obviously. I don't -- I'm learning. Executive functioning?

A. Right.

Q. Describe for me again what executive functioning refers to?

A. Well, Reader's Digest version is it's part of the brain's ability in an age appropriate way to plan, to organize, to quickly incorporate information learned in one setting to another one.

Q. Okay. That sounds important for maturation to adult life; you would agree?

A. I would agree.

Q. And just so I can picture this a little more. Is the Tower of London test

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basically like this child's toy that I've seen that you're rearranging disks to try to get them in a -- you don't know?

A. I'm not a neuroscientist or a neuropsychologist. I do know it can be done on the computer which is not going to be the same thing as hand-eye coordination.

Q. Now, this was -- so that we don't kind of over read it. If you turn to Page 192, it says that there were 41 adolescents with gender dysphoria in the study, 22 female to males. Some of whom had been subjected to puberty suppression and some who had not. And 18 male to females of which some had been subjected to puberty suppression and some had not. So all in all, it's a sample of 41; am I correct?

A. It's a very small sample, yes.

Q. And the mean time, if we turn to Page 194 at Column 1 at the end of the little Paragraph Number 3.1. It says the duration of suppression for male to females was 1.8 years. With the standard of deviation show ing it for female to males, it was 1.4 years. Do you see

Page 220

that?

A. I do.

Q. So would you consider that to be a long, short, or kind of standard length puberty suppression?

A. Fairly standard.

Q. And this is, if I understand correctly, not a longitudinal study. That is, it's a one-time study. Some of the subjects have been subject to suppression and some have not. But it's not a prospective study. It's not a longitudinal study, correct?

A. I believe so.

Q. Okay. If you look at 194, Column 1, towards the beginning of Section 3.1. It says, control boys, i.e., those who had not had puberty suppression, had significantly higher IQ scores than the suppressed male to females.

A. Okay.

MS. EAGAN: Roger, show me where you are.

MR. BROOKS: Paragraph 3.1, second sentence.

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MS. EAGAN: Thank you.

Q. (BY MR. BROOKS) And it's not longitudinal. But whatever report that those who had not experienced puberty suppression among the boys had higher IQ scores as measured by whatever test they use than males who had had puberty suppressed, correct?

A. That's what this sentence indicates, yes.

Q. And based on the nature of this study, that could be cause and effect or it could be a random variation between the control group and the study group, we can't tell?

A. It certainly could. What it indicates is that the case and control groups at the start may not have been equal for reasons we don't know.

Q. And if you turn back to Page 191 which is the -- not quite the first page.

A. Okay.

Q. In the abstract up top -- the abstract continues over from the previous page, and you certainly are free to refer to that part.

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It says on the first full sentence at the top of Page 191, it says, the suppressed male to females, if I may translate, had significantly lower accuracy scores than the control groups and the untreated female to males. Do you see that?

A. I do.

Q. And again, that potentially could be reflecting a negative impact of puberty suppression, but it could be reflecting other factors. We can't tell?

A. Correct. I read that the same way you do.

Q. Now, in a technical paper when the authors write that the accuracy scores of those boys who had been subjected to puberty suppression was, quote, significantly lower, that significantly is a term of art and refers to statistical significance, correct?

A. Correct, which is interpreted lightly with these very small numbers.

Q. Well, with small numbers, you would have to have a larger difference for it to be statistically significant, correct? That's how it

Page 223

works.

A. That may be how stats work, but it leaves someone reading a paper like this with -- you take it for what you see. But with very very small numbers, it may not be generalizable to an entire population.

Q. What do you understand to be the statistical -- the formal meaning of statistically significant?

A. It's been a long time.

Q. Something to do with P values?

A. Has to do with P values, greater than .05, less than -- depends on the test involved. But the question is the sample size, et cetera.

Q. Let me turn -- ask you to turn back to Page 194. In 3.2, which is headed Tower of London performance data. You're on the right page, 3.2.

A. Okay.

Q. 3.2, ToL, Tower of London performance data. It states that in the second sentence, Post hoc analyses show the suppressed

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male to females had significantly lower accuracy scores than the control groups and the untreated female to males. Have I read that correctly? I left one out. Let me try again.

Quote, Post hoc analyses showed that the suppressed male to females had significantly lower accuracy scores than the control groups, open paren, p equals .02 compared to control boys and p equals .04 compared to control girls, closed paren, and the untreated female to males. Closed quote. Do you see that?

A. I do.

Q. And again, the report here is that the treated subjects; that is, treated with puberty blockers had significantly lower accuracy scores on the Tower of London test than two different control populations, right?

A. That's what they're saying here.

Q. Well, you cited this paper. I assume that's because you thought it was a reliable scientific source?

A. I think it's the only source available at the time that has asked this question

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and done a bit to evaluate it.

Q. And by saying that the puberty suppressed boys, male to females had significantly lower accuracy scores, what that means is they just got the puzzle wrong more often than the control groups, correct?

A. I do not know. I've never administered a Tower of London test.

Q. I'm going to go home this evening and take one online and see how I do.

A. Let me know.

Q. If you look a little farther in that paragraph, it states, quote, even after correcting for IQ -- and we looked at IQ earlier -- a significant effect of group on accuracy remained. Closed quote.

A. Right.

Q. Do you think you understand that sentence?

A. Somewhat, yeah.

Q. What do you understand it to be telling us?

A. That even if you -- you can use

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statistical equations to control for the fact that one of these groups had an overall lower IQ. The findings can't. They didn't do as well on the Tower test.

Q. Let me call your attention to Table 1 on the next page, 193. And first I'll ask whether you studied this table of key results before you cited this paper in your expert report?

A. Not in intense depth.

Q. One of the things that's measured by the Staphorsius authors is reaction time; am I correct?

A. That's correct.

Q. And is that something that you understand generally improves across pubertal development?

A. I could not comment on that.

Q. Okay.

A. I've never administered a neuropsychological test to accept that point.

Q. I have watched my small children and my older children and as a layman, I suspect it's true, but I also don't claim to know.

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MS. EAGAN: Boys don't react real fast when they have to do something.

MR. BROOKS: That's a different question.

Q. The final column on this is RT which, am I correct you -- well, below the table it says RT, reaction times in seconds. So it's not a guessing game. RT is reaction time in seconds to whatever the test is. And if you look, we have the male to female suppressed and untreated. And do you see that the reaction time -- and pardon me. Let me ask a background question.

It is consistent with your understanding that when you're measuring reaction times, longer is worser?

A. Again, I'm not a neuropsychologist.

Q. Dr. Ladinsky, you cited this paper to say that there are no negative effects of pubertal suppression. Do you not know, quite apart from being a neuropsychologist, that a lower reaction time is less advantageous?

A. That's a generalized statement. I'm

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not sure I can generalize from the data presented here in the small groups information that may impact at this time in our history of clinical decision-making.

Q. Understood. It's a small sample?

A. Uh-huh.

Q. It's a one time rather than prospective?

A. Correct.

Q. But what they found in Staphorsius, et al., is that the reaction time of the puberty suppressed boys was slower than the untreated male to female boys and slower than the control's non-transgender boys, correct?

A. That is what they report.

Q. Which is, again, causation can't be determined from an experiment like this, but it's -- to the extent papers like this do anything, it raises a concern, does it not, that the puberty blockade may have, within the time period we have here, a negative effect on the development of reaction time?

MS. EAGAN: Object to the form.

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A. I don't read it that way.

Q. (BY MR. BROOKS) Why not?

A. My take from this is in the narrow scope of how it is conducted and carried out. It raises investigative questions, but it -- I don't see in it generalizability to come to the statement you made.

Q. If you don't see in this paper generalizability for all the reasons you explained, why did you cite it as evidence that Dr. Hruz was wrong in the concern that he raised?

A. "In conclusion, our results suggest that there are no detrimental effects of GnRHa on EF."

Q. I took you to data. If you don't believe the data is generalizable, why did you cite this paper as disproving Dr. Hruz' concern about potential impact on brain development from puberty blockers?

A. I put a bit more -- I utilized the authors' interpretation of their own data relative to the research question they asked. And the conclusion that they glean is what I took with me.

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Q. All right.
A. That sentence I read and, "We found no evidence for this and if anything, we found that puberty suppression even seemed to make some aspects of brain functioning more in accordance with natal sex."
MR. BROOKS: I'd like to mark as Exhibit 24 a scientific statement from the Endocrine Society dated 2021 entitled "Considering Sex as a Biological Variable in Basic and Clinical Studies."

(Whereupon, Ladinsky Exhibit 24 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, you've repeatedly referred to the Endocrine Society Guidelines relating to treatment of gender dysphoria. This is a different document from the Endocrine Society. And I'll ask first whether you think you've ever seen it before?
A. I do not recall seeing this document

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before.
Q. I am going to ask you about one scientific proposition that it states. If you would turn to Page 238. Before that let me ask: Are you generally aware of a requirement from the NIH, the National Institute of Health, that studies that they fund must consider sex as a biological variable; that is, they need to separately record data with respect to male or female individuals or even male or female cells in whatever the experiments are?
A. I'm not aware of that, sir. I'm not a researcher.
Q. Would you look on Page 238, Column 2. And 3 inches down from the bottom -- 3 inches up from the bottom -- pardon me -- is a sentence that begins "Recent evidence." It's a buried sentence. "Recent evidence has revealed."
A. Okay.
Q. Let me read that into the record. Quote, "Recent evidence has revealed that molecular sex differences in the brain are more widespread than initially thought and such

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seemingly small-scale differences can have a large impact on physiology and behavior. Neurons typically communicate with each other via neurotransmitters and neuropeptides, which are released presynaptic neurons and travel across a synapse to bind receptors on the postsynaptic neuron to exert downstream cellular effects. There are sex differences in production and release of many neurotransmitters and neuropeptides that can result in behavioral changes."
First, let me ask at a high level: Is it within your knowledge that in recent years science has discovered more and more differences down to the cellular levels between male and female brains?
A. I'm not aware of that.
Q. You're not aware of that?
A. But again I'm not a --
Q. I understand.
A. -- psychologist or researcher.
Q. And you don't have any knowledge as to whether it's true or not true that sex-based

Page 233

differences in human brains go even to the level of neurotransmitters and neuroreceptors?
A. Not in detail, no.
Q. It is within your knowledge, is it not, that every brain -- every cell in a human brain contains either XY male chromosomes or XX female chromosomes in a normal healthy human?
A. Unless there's a genetic or receptor based disorder of sexual development.
Q. Hence my qualification, normal healthy human.
A. Okay.
Q. You would agree with the statement?
A. I guess.
Q. Well, every cell in your brain is female in the sense of having an XX chromosome, and every cell in my brain is male in the sense of having an XY chromosome, correct?
A. If you say so, yeah.
Q. No. I'm asking you. You're the witness.
A. I believe so.
Q. And are you aware of any study ever

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of the effect on brain function and health of flooding a male brain with estrogen levels that never occur in a healthy male and could never naturally occur in that brain?

A. Again, I'm certainly -- I'm not a researcher, and I'm not encyclopedic in the literature relative to basic science studies.

Q. If you have no knowledge as to the effect of flooding a male brain with female hormones at levels that could never naturally occur in that brain, on what basis do you assert that administering cross-sex hormones is safe?

A. If we take a step back -- and I think why this question was so difficult for me even though it seems easy is that as physicians we don't -- pediatricians we don't think about brains as male brains or female brains. They're just that child's brain. So that's why it was hard for me to answer this question. Even outside of gender health, we don't think of child development as boy brain, girl brain. We think of it as that child's brain. So with that caveat, it's a little hard -- that's why it was harder to answer that one.

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Q. Is it your professional opinion that experts in child development don't think and don't research in terms of boy brain and girl brain?

A. Those are just not terms that are familiar to me nor have I seen them in the literature I read.

Q. In fact, you're well familiar with literature that documents that boy brains and girl brains follow different developmental trajectories and are well recognized in repeatable fashions, are you not?

A. Give me some examples.

Q. No. I ask questions only.

Are you or are you not familiar with such literature?

A. That boy brains and girl brains develop differently at different times?

Q. Yes.

A. That's not --

Q. Indeed that they develop in physically different ways identifiable by MRI scans?

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A. I'm not aware of it on the level that you're discussing.

Q. Let me ask you to turn in your expert report to Page 7, where in the first full sentence on the page you wrote, quote, "All the major medical professional groups in the United States, including the American Academy of Pediatrics, the American Medical Association, and the American Academy of Child and Adolescent Psychiatry, agree that this care is safe, effective, and medically necessary treatment for the health and wellbeing of children and adolescents suffering from gender dysphoria." Closed quote. Do you see that?

A. I do see that.

Q. And in writing that, did you go check and ascertain that these organizations had actually represented that these treatments were, quote, "safe"?

A. I believe -- not sure how you're defining safe or how they're defining, but I know that all three of these organizations -- three here -- endorse this care --

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Q. Did you --

A. -- as safe, effective, and medically necessary for the health and wellbeing.

Q. You cite the Endocrine Society Guidelines?

A. Right.

Q. Let me ask you to turn to that which is Tab 37 in your binder.

A. Okay.

Q. Do you believe that you found any representation from the Endocrine Society in this document that either puberty blockers or cross-sex hormones are safe when administered to adolescents?

A. If you give me your definition of safe that would be great --

Q. No.

A. -- to help me.

Q. You represented in your expert report that these organizations had stated that it was safe. So we'll work with your -- whatever you meant when you said that.

Do you think you looked for and

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found any such representation before making that statement in your report?
A. I think endorsing a specific line of treatment carries that notion within it. In other words, everything in medicine is a cost-benefit evaluation application to an individual patient, but I certainly did not see in any of these guidelines a statement that this treatment is unsafe.
Q. You did see statements in the Endocrine Society Guidelines raising concerns that puberty blockers could affect brain development, did you not? We looked at that earlier.
A. Yeah. They raise it as a possibility, though they don't cite solid evidence. And they raise it as a question for research.
Q. And you did see reference in the Endocrine Society Guidelines to a number of other known or potential adverse effects of both puberty blockers and cross-sex hormones for adolescents, did you not?
A. Correct.

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Q. And what you didn't see anywhere in the Endocrine Society Guidelines was a statement that either of those treatments was safe when administered to adolescents, did you?
A. We think about that term in a clinically relevant way. In other words, when weighing risk versus benefits for an individual patient, there is a level of safety. And we have data, the use of these medications in similar ages for other indications.
Q. That's you. But what you can't do is point me to anything in the Endocrine Society Guidelines that represent to the world that these treatments are safe when administered to children or adolescents; is that correct?
A. I'm not sure that that sentence exists in here.
Q. All right.
MR. BROOKS: Let me mark as Exhibit 25 a paper by Rafferty headed "Ensuring Comprehensive Care and Support For Transgender and Gender-Diverse Children and Adolescents" dated 2018.

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(Whereupon, Ladinsky Exhibit 25 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Dr. Ladinsky, this is the AAP statement that you cited in support of your representation that the AAP has asserted that the use of puberty blockers and cross-sex hormones are, quote, "safe"; am I correct?
The question on the table is --
A. This is the policy statement to which I referred, yes.
Q. Okay. I have searched with the benefit of an online search key --
A. Tool.
Q. -- and I can't find any assertion by Rafferty, the AAP, that either puberty blockers or cross-sex hormones are safe when administered to children. Do you believe that you found such before making that representation in your expert report?
A. When endorsing -- again, when a

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consensus body endorses a modality or a treatment protocol or paradigm, within that is data reflecting on relative safety that doctors take into consideration in the cost-benefit analyses with patients. You will not find that single sentence in there.
Q. Have you yourself participated in developing such a medical association statement?
A. This? No, I have not.
Q. Any such?
A. No, sir.
Q. How do you know how -- and by the way, do you have any knowledge as to who participated in preparing the AAP statement?
A. So not only Dr. Rafferty, but you had a lot of input from members of two different, what we call, AAP heads, bodies, sections, and committees. So you had a number of people from the committee on psychosocial aspects of child and family health, the adolescent health, and then the section on LGBTQ.
Q. Do you have any personal knowledge as to what input, if any, any of those individuals

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had?
A. I do.
Q. And on what bases?
A. I'm a member of the section on LGBTQ health and wellness. I'm also a member of the minority health equity and inclusion subcommittee, and so --
Q. Prior to 2018, you --
MS. EAGAN: Were you through with your answer? I thought you interrupted her. I. Wasn't sure if you were you through with your answer because you said, "and so -- ".
A. But I was going to say I know the processes by which these policy statements are arrived at. There is a lot of member input.
Q. (BY MR. BROOKS) In general, multiple members would review such policy statements? Multiple members would have a hand in revising it perhaps?
A. That's correct.
Q. It would have to be approved by the entire committee or multiple committees?
A. That's correct, yes.

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Q. All right. But just to be clear, your citation of -- so far as you recall, your citation of the Rafferty paper was not based on finding any representation in Rafferty that puberty blockers or cross-sex hormones were safe as administered to adolescents, but rather you inferred that from the endorsements of those procedures?
A. That's a relative sort of inference, but that is inherent in how physicians interpret, align with, utilize policy statements like these and other standards of care and guidelines.
MR. BROOKS: Let me mark as Exhibit 26 a document headed "AACAP Statement Responding to Efforts to Ban Evidence-Based Care For Transgender and Gender Diverse Youth" dated November 2019.

(Whereupon, Ladinsky Exhibit 26 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Did you review this

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document preferably before citing it for the proposition that the AACAP had stated that use of puberty blockers and cross-sex hormones was, quote, "safe"?
A. AACAP being the American Academy of Child and Adolescent Psychiatry, correct?
Q. I take your word for it, yes.
A. No. I've not seen this document, but I'm well aware of the endorsement from this organization.
Q. Well, let me ask: You cited in your footnote a November 8, 2019 statement from the AACAP. This is a November 8, 2019 statement. I'm sorry. Maybe I misspoke. This is the date you cited in your footnote, and yet you say you've never seen it before?
A. I'm sure I've seen it in putting this together, yes. Actually, yes.
Q. Did you or did you not review this document before citing it in your expert report?
A. I did review it.
Q. And did you find any statement from the AACAP that these hormonal interventions in

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minors are, quote, "safe"?
A. I do not see a sentence that states that.
MR. BROOKS: Let me mark as Exhibit 27 a document headed "AMA, State Advocacy Update". March 26, 2021.

(Whereupon, Ladinsky Exhibit 27 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) And is this a document that you cited in your footnote in support of the proposition that medical organizations had endorsed hormonal interventions as, quote, "safe"?
A. Quite honestly, possibly. I know that there are other -- and that's perhaps yes.
Q. Well, I didn't --
A. There are other AMA documents that go into more detail.
Q. If it's -- I don't want to make a mistake on this. So behind Tab 13 is your expert

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report. Let's double-check whether that's what you cited.
A. That's a fair statement.
Q. Okay.
A. It's a summary of -- what I'm seeing in my head is a more lengthy document.
Q. And you are not expressing the view that this advocacy update is something that was voted on by the membership or by any formal committee of the AMA, are you?
A. I'm sorry. Can you restate that?
Q. Yes. You don't have any opinion as to whether this advocacy update was voted on by any committee of the AMA, do you?
A. I'm not aware of the details within the AMA. I'm quite aware of the AMA's disdain for criminalizing health for transgender minors.
Q. And do you believe that you can point me to any statement in this document from the AMA that hormonal interventions in minors are, quote, "safe"?
A. No, sir. And that's not the point of this document.

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MS. EAGAN: Roger, when you get through with this line of questioning, can we take a break? We've been going for a long time.
MR. BROOKS: Let's do a break. I'm at the end of that line of questioning.

(Whereupon, a brief recess was taken.)

Q. (BY MR. BROOKS) New topic.
A. New topic. Okay.
Q. Would you agree with me that biologically a key, almost defining, aspect of puberty is development into fertility. That is the individual becoming potentially fertile? It's not a mysterious question.
Would you agree with me that a key, almost definitional, aspect of the pubertal process is a child sexually maturing to become potentially fertile?
A. That is a longitudinal aspect of the physiologic changes that happen during puberty.
Q. And specifically, puberty includes

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gonadal and hormonal changes that are necessary to achieve fertility?
A. In today's world not necessarily, but.
Q. I'll ask a more precise question. Natural healthy puberty includes gonadal and hormonal changes necessary to achieve fertility, correct?
A. Ideally.
Q. Let's go back to the Rafferty paper, Exhibit 25. And you cited this in your expert report because you believe it to be a generally reliable document?
A. Generally reliable, what do you mean?
Q. In your opinion is the description of the science a description that you can rely on as a clinician?
A. I think that's fair.
Q. Let me ask you to turn to Page 6. And there is a Table 2 at the top of the page that says -- titled "The process of gender affirmation may include one or more of the following

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components."
A. Right.
Q. And puberty blockers -- one of the columns is reversibility, right? You see that?
A. Right.
Q. And puberty blockers, it says reversible and then has a little footnote.
A. Little C.
Q. If we follow that C, what it says is, quote, "The effect of sustained puberty suppression on fertility is unknown." Do you see that?
A. I see that. It's Footnote C.
Q. Footnote C?
A. Yeah.
Q. And do you agree or disagree with the American Academy of Pediatrics or is it outside your expertise to say that the effect of sustained pubertal suppression on fertility of the adolescent is unknown?
A. I think the remainder of that and then Footnote 6 of 68, and they refer, yeah, right back to the Endocrine Society Clinical Practice

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Guidelines. So I think that's the way that it's stated here. And in Footnote C, I don't have any problem with that.

Q. That is, you don't disagree with the statement that the effects of sustained puberty suppression on fertility is unknown?

A. I don't have any -- I agree with that statement. The question is: What does the Endocrine Society and Dr. Rafferty and our clinical judgment mean by sustained?

Q. Let's look at what the Endocrine Society has to say since you mentioned that, and that is in your binder, Tab 37. And I'm going to call your attention to Page 3880, but you're going to want to look back and see what recommendation this discussion pertains to which is on the previous page, 1.5. And what that recommendation says is, quote, "We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the

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affirmed gender in both adolescents and adults." Closed quote. Do you see that?

A. I do.

Q. And do you have any understanding if puberty suppression is simply a pause why the Endocrine Society recommends counseling regarding options for fertility preservation prior to administering puberty suppression?

A. I do believe that section -- this recommendation Number 1.5, "The task force placed a high value on avoiding harm with gender-affirming hormone therapy in prepubertal children with GD/gender incongruence." That's -- so that's the sentence that proceeds it.

Q. Yes.

A. Meaning prepubertal children are not prescribed medication. That is the standard of care. They're talking in generalizable terms, puberty suppression and prior to treating with hormonal therapy. They're talking about the entire manuscript there.

Q. Well, they speak specifically about providing counsel for options fertility

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preservation prior to initiating puberty suppression in adolescence. Do you see that?

A. I do.

Q. And if puberty suppression just acts as a pause, do you have any understanding why the Endocrine Society recommends that clinicians provide counseling on fertility preservation prior to administering puberty blockers?

A. I can only infer. But for youth who begin puberty blocker medications and then over a period of time maintain sustained significant dysphoria becoming eligible for hormonal therapy, okay, that discussion must be had because there is a possible decrement to fertility in that group.

Q. For a child who's put on puberty blockers at, let's say, 10 or Stage 2 and proceeds without interruptions onto cross-sex hormones, there are in fact no options for fertility preservation, are there?

A. There are.

Q. What demonstrated options for fertility preservation in that context are there?

A. If that young person were to allow

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for a little bit of space in between, it can be obtained.

Q. That is if the child -- that's contrary to my hypothetical, so let's break it down.

My hypothetical was a child is put on puberty blockers at 10 or Stage 2 and proceeds without interruption to cross-sex hormones at whatever age you generally consider to be clinically appropriate, for that individual, there are no fertility preservation options, are there?

A. I'm not -- remember I'm not a reproductive endocrinologist. However, in the future that person, if they, you know, cease their treatment for a little while, may be able to procure gametes. But I think the Endocrine Society makes this recommendation in a very general way here, and it's a sound board.

Q. Now, they mentioned in the little heading, values of preferences, that you just stated, that -- I take it from the way they stated, that all the evidence relating to fertility is, quote, what they call "low-quality

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evidence", correct?
A. Everything, all of it throughout the whole document?
Q. Everything on which they base their recommendation they describe as low-quality evidence; am I right?
A. They say right here, okay, "This justifies the strong recommendation in the face of low-quality evidence." But I think it's important to understand the context around this term "low quality", "lesser quality", et cetera. That does not refer to utilizing, not utilizing, negating the recommendation. That term "low-quality evidence" simply refers to the studies that undergird that recommendation and how their methodology aligns with randomized prospective double-blind placebo-controlled. These are terms that physicians and clinicians use in interpreting evidence. The notion of low quality is more of a technical term referring to study methodology. Not bad, good, horrible, yucky.
Q. Technical terms, right?
A. Yes, sir.

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Q. So if we turn over the page, we're still on the discussion of the remarks about use of puberty blockers.
A. Okay.
Q. And at the top of Column 388 -- of Column 1 of 3880, the first full sentence reads -- and we're talking here about males as will be obvious. "Note that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility." Do you see that?
A. Right here. I do see that.
Q. And this is -- that population refers to boys who have been on puberty suppression for a period of time and then ceased puberty suppression for a period of time, correct?
MS. EAGAN: Dr. Ladinsky, I would ask that you read -- I would like for her to read all these remarks leading up to it because you're asking about one sentence.
MR. BROOKS: That's fine. I already thought she had, basically.
MS. EAGAN: I'm not sure she has.

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A. I've read it, but, I mean, it's important to know that this is in a section, recommendations for those involved in the gender hormonal treatment of individuals. It's not a single section on puberty blockers.
MS. EAGAN: What I would ask, though -- read the remarks, Dr. Ladinsky. Take your time to read the remarks and then answer his question about the context of that one sentence, please.
A. Okay.
Q. (BY MR. BROOKS) All right. At the -- referring to the population of natal males who have been on puberty blockers, it says at the top of Column 1, quote, "There are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility." Closed quote. Do you see that?
A. I see that.
Q. So far as you know, is it still true that there is no data on that topic?
A. While I am not a researcher --

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remember this was 2017.
Q. That's why I asked.
A. There is considerable work ongoing not just in the field of gender health but more importantly in pediatric oncology where nothing to do with gender, this population may need to enter into chemotherapeutic regimens that could later impair fertility. And there is a good amount going on right now to find, you know, to give us a better idea. But you see right there .7 to 3 years.
Q. I'm sorry. What was -- I see.
A. In the next sentence because --
Q. This is in a different use case; that is, in adult men --
A. No. In males treated for precocious puberty.
Q. Pardon me. Yes.
A. Spermarche means the ability to obtain viable sperm from a sample from that patient. 0.7 to 3 years after cessation of GnRH analogs.
Q. So --

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A. Puberty blockers.
Q. So far as you know, there's been no study of how long it takes or whether an individual whose puberty -- whose ordinary endogenous puberty has been blocked can generate enough sperm to use the language here, quote, "for later fertility," closed quote?
A. I think you see it right here. 0.7 to 3 years after cessation, after stopping the blockers.
Q. That doesn't make any representation about whether there was enough to achieve fertility, does it?
A. Well, spermarche implies that.
Q. Is that your understanding of the literature?
A. No. Looking at the term.
Q. I understand.
A. The ability to collect viable sperm.
Q. Do you know whether in the literature spermarche implies actually fertility?
A. I do not, but.
Q. And as to another use case; that is,

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adult men with gonadotropin deficiency, it notes that sperm numbers were quote, "far below the normal range", correct?
A. I don't take care of adult men with gonadotropin deficiency.
Q. You don't prescribe puberty blockers for children with precocious puberty either, do you?
A. My endocrinology colleagues do.
Q. And what the Endocrine Society says is that in the case of adult men who have for whatever medical reason been subjected to blockade, after some period of time it remains true that their sperm numbers are, quote, "far below the normal range", right?
A. That's referring to this unique population of men. That's how I read it.
Q. And you wouldn't want to extrapolate from that population to adolescents who have had puberty blocked at its normal healthy time, correct?
MS. EAGAN: Object to the form.
A. Let me just look at -- if you don't

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mind, 70 and 71, I'd like to look at this footnote.
Okay. Both of these studies were looking at a different population of adult men who for exactly as you said, reasons we don't know, are gonadotropin deficient.
Q. And my question was simply: You don't think it's appropriate to extrapolate from the experience of that population to what the experience may be of adolescents who have normal healthy puberty blocked?
A. Not in a clinically significant way for me on a frontline.
Q. And for similar reasons, it would also not be appropriate to extrapolate from a population that suffered from precocious puberty and had puberty blocked -- and had puberty occur at -- postponed until, I should say, a normal time period for puberty?
MS. EAGAN: Object to the form.
A. On the contrary, I think that's immensely helpful. It gives me information about pediatric patients who began the same treatment at

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the same physiologic stage.
Q. (BY MR. BROOKS) So let me ask you about physiologic stage. It's not your testimony, is it, that children who suffer from precocious puberty are at the same brain developmental stage as children to whom your team prescribes puberty blockers as a treatment for gender dysphoria?
A. Some may be. I can't state, you know, that's a yes or a no.
Q. I would have thought you could.
A. It's a wide range.
Q. So let me ask: Precocious puberty, how do you understand that to be defined?
A. Precocious puberty in a natal male is the development of secondary sex characteristics or adrenal ketones under androgen before the age of 9; and in a girl, before the age of 8. Again, androgenic, not breast buds, but other elements.
Q. And if that was happening, for instance, in a boy at age 8 and a girl at age 7, would your hospital potentially prescribe puberty blockers?

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A. They may.
Q. For that small advance?
A. They may.
Q. It is not your testimony, is it, that on average children who suffer from precocious puberty are at a level of neurological development comparable to the average level of development of children for whom you prescribe puberty blockers as a treatment for gender dysphoria?
A. If by brain development you mean they're a few years on average younger, that's true.
Q. And to your knowledge, important aspects of brain development routinely occur during those few years, correct?
A. Important aspects of brain development occur at all ages.
Q. And it's not your testimony, is it, that on average children who are prescribed puberty blockers as a treatment for precocious puberty have physical size and body development comparable to children for whom you prescribe

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puberty blockers as a treatment for gender dysphoria?
A. On the contrary they often may. They may have the same height.
Q. I didn't ask may. I said on average.
A. I think it's quite common. Precocious puberty puts them at a physiology, including size, on par with someone who may be eligible to receive puberty blocking medication for significant gender dysphoria in early adolescent Stage 2.
Q. A little farther down in the column on 3880, it says in the next paragraph, "In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function." However, in the next sentence it says, "Clinician should inform adolescents that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogs or the response to ovulation induction following prolonged gonadotropin suppression." Do you see that language?

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A. I see it.
Q. And is it still consistent with your understanding that there is no data out there about how long after cessation of puberty blockers a girl may resume ovulation?
A. At the moment, there are no data available at the time of this report. And if there are data looking specifically at the timing of eventual ovulation for someone assigned female at birth that was placed on GnRH analog for central precocious puberty or for gender dysphoria. I do not know if there have been data since that. I do know that there's long-term data in cisgender females treated with GnRH analogs for central precocious puberty that report normal pregnancy, ultimate fertility, et cetera.
Q. So as far as you know, there are no data with regard to females treated with puberty blockers to prevent normal healthy timed puberty as to when, if ever, those girls can achieve healthy levels of fertility?
A. It would -- I mean, to me that's a two-part question that would also -- are we

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looking at a population of theoretical girls that did begin puberty suppression at 10 or 2 or early 10 or 3 and then took a pause to maturation before beginning hormonal therapy; or are we talking about girls that go straight.
Q. In neither case is there any data to your knowledge as to when or whether those girls can ever achieve healthy levels of fertility?
A. As to whether I believe, there may be. There's some data showing that if they stop -- stopping testosterone or decreasing, fertility is quite possible.
Q. Well --
A. There's also --
Q. Go a little bit further down here.
A. -- many cases of trans men becoming pregnant, intended and unintended.
Q. It says -- at the end of the paragraph -- it says in the third paragraph, restoration -- and now we're talking about cross-sex hormones. "Restoration of spermatogenesis after prolonged estrogen treatment has not been studied." Period. Do you see that?

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A. At the timing here, it had not been studied.
Q. And so far as you know, it has still not been studied, correct?
A. I believe -- I'm no expert and I'm not an endocrinologist, a reproductive endocrinologist. But there is some data showing that even after prolonged estrogen treatment, restoration of spermatogenesis, quite possible.
Q. Do you have any study in mind when you say that or a statement from any organization?
No consulting with counsel on that.
A. All right. I would need to look into it.
Q. As you sit here now, you don't recall?
A. I'm telling you anecdotally, I can't give you an exact reference.
Q. Do you have a specific case from your clinic's experience in which a natal male who underwent prolonged cross-sex hormone treatment has subsequently become a father?
A. No, sir. Our clinic hasn't been

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around long enough for that to have taken place.
Q. Are you aware of any report of such a case in the literature?
A. Not that I can specifically direct you to.
Q. And anybody that you've treated in your clinic -- and if you started at 15 perhaps, they would be --
A. 23.
Q. -- 23. Just old enough. Are you aware of any case in which a natal female who underwent prolonged treatment with endogenous testosterone has later conceived and born a healthy child?
A. Yes.
Q. In one of your patients?
A. No, sir. Our patients aren't that old. Our first cohort are in college.
Q. And what case did you have in mind when you said yes, sir?
A. This is a case of an adult male, an adult trans man, that a colleague of ours -- not -- in a different state. A colleague of ours

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had brought to our attention where this man, transgender man became pregnant unintentionally but very happily and gave birth to a very healthy baby boy.
Q. What do you know about what hormonal or puberty blocking treatments that natal female had been subjected to prior to that pregnancy?
A. I do not know that gentleman's entire medical history. This was a case that a colleague had elevated in a discussion section with many of us, so I do not know a thing about that gentleman's history nor is it my business to know. However, he is far from the -- he's far from the only one.
Q. All right. Tell me another one.
A. Many adult trans men do carry their own children.
Q. Many adult trans men, natal females don't in fact choose to undergo cross-sex hormones, correct?
A. I couldn't speak to any individual's preference choice or how they manage their gender care.

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Q. General question.
A. Right.
Q. Many natal females who choose -- who live in a transgender male identity choose not to take cross-sex hormones; am I correct?
A. I think it's fair to say that transgender adults as a group may or may not choose to take or to continue hormonal therapy.
Q. So when we see a news item about a transgender man who has conceived and borne a child, we just don't know anything about whether that individual ever was subjected to prolonged testosterone, exogenous testosterone treatment, do we?
A. We don't know each individual man's medical history.
Q. And you're not aware of any published case study that documents a natal female who has been subjected to prolonged exogenous testosterone who has conceived and borne a healthy child?
MS. EAGAN: Object to the form.
Q. (BY MR. BROOKS) You can answer the

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question.
A. If you give me a computer, I can find you one, but I can't point you to one right now. That does not mean it has not been studied or that case collections have not been assembled.
Q. I understand. Part of my function today is just to get clear what you know and what you don't, and others may know other things. We put puzzle pieces together.
MR. BROOKS: I'm going to mark as Ladinsky Exhibit 28 a transcript of the PI, preliminary injunction hearing testimony of Dr. Antommaria from May 6, 2022.

(Whereupon, Ladinsky Exhibit 28 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) On Page 231 of this transcript, Dr. Antommaria was asked, "Would you agree that some of the risks of puberty blockers and cross-sex hormones would be loss in fertility?" And Dr. Antommaria answered, "There

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is a risk of impaired fertility."
Let me just ask you: Do you agree with Dr. Antommaria on that point, do you disagree, or do you think it's really outside your expertise?
A. If we are allowed to start at Sentence 8, I fully agree with Dr. Antommaria's bolded 8 through 11. And then as it continues with reference to some of the risks of puberty blockers and cross-sex would be loss of fertility. I agree with Dr. Antommaria's statement of, "There is a risk of impaired fertility."
Q. All right. Let's look at a very recent statement because you referred to a number of times of the possibility of more recent research. And I will take you to Exhibit 20 which is the de Vries editorial in the New England Journal of Medicine if we can find that. And I'm just going to take you back to language that we actually read into the record earlier, but we were focusing on brain development. The second page, the second column, two-thirds of the way down, it reads, "Finally, benefits of early medical

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intervention, including puberty suppression, need to be weighed against possible adverse effects, for example, with regard to bone and brain development and fertility." Period. Closed quote.
A. Right.
Q. And if Dr. de Vries of Vrije University team, writing in 2023, expresses the view that adverse effects on fertility are still possible effects of puberty suppression and early medical intervention, then do you agree, disagree, or think that you lack information to form an opinion on Dr. de Vries' statement?
MS. EAGAN: Object to the form.
A. Dr. de Vries is simply, to me, articulating what is done clinically on the frontlines which is weighing no risks, unknown risks, known benefits in the context of each individual patient.
Q. (BY MR. BROOKS) And one of the risks that Dr. de Vries thinks as of 2023 needs to be weighed is the risk of impairing fertility, correct?

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MS. EAGAN: Object to the form.
A. Correct. That is what Dr. de Vries says right here.
Q. (BY MR. BROOKS) Let me ask you to turn to your expert report to Paragraph 21. Maybe it's Page 21. You don't have numbered paragraphs. Page 21. Tab 13.
You state four lines from the bottom, quote, "Many people undergo fertility preservation before any treatment that could compromise fertility."
Of -- and you've said that the preponderance of the patients who present at your clinic are 14 years or older?
A. Correct.
Q. And among natal girls, what proportion who are age 14 have experienced menarche and are producing potentially fertile eggs?
A. Many.
Q. Many?
A. Yeah.
Q. What proportion of young people who

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come to your clinic into adolescence -- we'll talk about those 17 that you've given puberty blockers to. What proportion of those who arrive late enough that that's not an issue in fact undergo fertility preservation techniques before you administer cross-sex hormones to them?

A. Similar to Dr. Antommaria, I'd like to desegregate my trans ladies, natal males, from my trans men, natal females.

Q. Please.

A. Okay. And with reference to the former.

Q. Natal males?

A. Natal males identify female and those who go on to begin cross-sex hormones as older teens, those trans ladies. Following, you know, lengthy discussions leading up to that, more than half --

Q. Okay.

A. -- do bank gametes.

Q. And now for the natal females?

A. For the natal females, so those assigned male -- assigned female at birth identify

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male --

Q. I'm glad you get confused too.

A. -- that are beginning testosterone therapy. The preponderance of the evidence is such that as adults they are not as likely to experience impaired fertility should they want to, you know, one day have their own biologic children. So again, medicine, cost-benefit rate, the evidence showing that should they want to as adults either stop testosterone; if they have a uterus, carry their own child; relative to the procurement of eggs, which is extremely costly and quite invasive. It's cost-benefit given the family, the information we have, but it's not common that that's chosen.

Q. I think we saw earlier in the Endocrine Society document their representation that there was in fact no data on recovery of fertility by natal females after prolonged exposure to testosterone. You recall that?

A. That was a statement in 2017.

Q. And when I asked for more recent information, you referred to things you had seen

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in the news rather than anything in the scientific literature?

A. I didn't say that, sir.

Q. I thought you did?

A. Something I'd seen in the news?

Q. Then let me --

A. No, sir.

Q. Then let me ask: Are you aware of any peer-reviewed report, whether a study or a case study, of a natal female who has conceived and borne a healthy child after an extended period of years on cross-sex testosterone?

A. I have reason to believe that data exists. I cannot encyclopedically procure it for you out of my head, though.

Q. Despite the fact that you can't identify any such study, you advise natal females that fertility preservation is not so urgent for them because they will be able to have a better chance of recovering fertility later in adulthood if they change their minds?

A. It is not said exactly like you said that in counseling family.

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Q. How do you say it?

A. We talk about the risks of impaired fertility as adults should they maintain a uterus and want to carry their own biologic children and the possible need for fertility -- assisted fertility should that occur. We talk about the banking of ova and what is involved. And families weigh that and make their decision accordingly.

Q. When you say assisted fertility, what do you refer to?

A. The need to visit a reproductive endocrinologist later in life.

Q. But again, up to the present, you haven't seen a specific case study of any natal female who has been on cross-sex testosterone for a period of years who has conceived and borne a healthy child even with the assistance of a reproductive endocrinologist, correct?

MS. EAGAN: Object to the form.

Q. (BY MR. BROOKS) Unless she instructs you not to answer, you still have to answer.

A. I'll just restate what I just told

you.

Q. Then let me ask her to read the question first, and then you can decide whether that's what you need to do.

(Whereupon, a portion of the testimony was read by the court reporter.)

A. I cannot point you to such a study. It does not mean it is nonexistent in the literature, the popular literature as well as the medical literature.

Q. (BY MR. BROOKS) Let me ask you to turn to Page 27 in your expert report. And you say -- there's a paragraph, full paragraph here that leads into the discussion of bone density. Do you see that?

A. I do.

Q. And you say towards the end, quote, "we know from excellent data that bone density catch-up ensues. This is well documented and matches our own clinical experience." Do you see

that?

A. I see that.

Q. And for well documented -- well, let me ask you first about your clinical experience; that is, do you routinely measure the bone density of young people in your practice before and after they take cross-sex hormones or puberty blockers?

A. We do not routinely unless they have -- remember, we use puberty blockers for short durations of time. If they have other medical indications or other medical challenges that could interfere with calcium metabolism, vitamin D metabolism, or bone density, we do. But at this point, there is not -- it's not for these brief periods of time.

Q. In your clinical experience, you haven't compiled quantitative data about bone density, correct?

A. No, sir.

Q. So now let's look at what you say in Footnote 20 which is van der Loos.

MR. BROOKS: Let me mark as Exhibit 29. I think this will be called a research

report, a short thing by van der Loos.

(Whereupon, Ladinsky Exhibit 29 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) And this is titled "Development of hip bone geometry in transgender adolescents resembles the experienced gender if GnRHa treatment is started in early, but not late, puberty." Do you see that?

My initial question is: Am I correct that this is what your Footnote 20 refers to?

A. I am -- but I believe that if you see that the original publication was in the Journal of Bone and Mineral Research, and this is in The Journal of the Endocrine Society. I believe that this is sort of a concise summary of that article as sort of abridged and published in the Journal of Endocrine Society, not the original.

Q. That's probably right and I'll have

to follow that link there for the exciting --

A. Sorry.

Q. -- completion of this installment. Okay. I will not take your time on what's not the right document.

MR. BROOKS: Why don't we take a five-minute break while I kind of do a final scan.

(Whereupon, a brief recess was taken.)

Q. (BY MR. BROOKS) Let me ask a process question. As you prepared your expert report, did -- and without going into the substance, did counsel assist you, by for instance, in identifying articles that you might find useful to cite?

A. I think that's fair.

Q. And did counsel provide any editorial suggestions to the text?

A. It was a sort of back-and-forth if that makes sense.

Q. That does make sense.

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A. Okay.
Q. And did you ever take care that by the end everything in this report reflects your opinion rather than the opinion of counsel?
A. Yes, sir.
MR. BROOKS: Let me mark as Ladinsky Exhibit 30 a document entitled "Patient information for informed consent feminizing medications for transgender clients," which was apparently marked as Plaintiff's Exhibit 41 at the preliminary injunction hearing.

(Whereupon, Ladinsky Exhibit 30 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) And Dr. Ladinsky, I read the title that you see here. It's several pages in, you will see also the document -- it's probably in -- sometimes a separate document -- client information for informed consent, testosterone for transgender clients. I just want you to understand what we have here.

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A. So I'm assuming I have both -- okay.
Q. And I've just marked it as it was used as an exhibit at trial. I just want you to be aware that both of those are in here.
And does this -- do these two documents, if I may, are these still the forms that you're using in your clinic today?
A. They are.
Q. And when was the last time any change was made to these documents?
A. I believe they were reviewed, reformatted in the lead-up to the PI hearing.
Q. Was the substance changed as far as you know?
A. No, sir.
Q. And any of the specific disclosures changed in the lead-up to the PI period?
A. Not to my knowledge.
Q. So the first document refers to feminizing medication, and then the second one refers to testosterone for transgender clients. Neither of those categories include puberty blockers; am I correct?

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A. Correct.
Q. And do you have a different informed consent form that you use prior to administering puberty blockers?
A. So we actually do not use a written informed consent form for puberty blockers, and that's in line with the practice in many centers around the country. We at our center view them as a reversible but sort of pause button. We do in each patient's chart have, you know, basically a summary of what we discussed with the patients relative to potential side effects, intended effects, et cetera, of puberty blockers.
Q. Well, do you have any script that you or people associated with your clinic use to make sure that they have raised all potential side effects of puberty blockers in those oral conversations?
A. We do.
Q. And what does that look like? How long a document is it?
A. It's -- I'm visualizing it sort of as a phrase in the medical record. But it's a

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paragraph like that (indicating).
Q. It's not more than a page long?
A. That's fair.
MR. BROOKS: Counsel, I will say that I believe that that document is clearly called for by the document request, and we will request that it be produced following up.
MS. EAGAN: Well, I'll say I'm not UAB's lawyer, so you'll have to take that up with UAB's lawyer.
MR. BROOKS: Quite so.
Q. We will follow up on that.
A. Sure, absolutely.
Q. I appreciate your assurance.
A. Remember that the UAB Gender Health Clinic --
MS. EAGAN: There is no question on the table.
THE WITNESS: Okay.
Q. (BY MR. BROOKS) I like to think the Gender Health Clinic is not using puberty blockers, but that's a separate question.
A. Ditto.

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Q. All right. Let me just ask you about Page 3 of this document. And I'm looking at the information for feminizing.
A. Okay.
Q. You specifically require -- at the bottom of this page it states, "I know that there may be mood changes with these medicines, and I agree to continue therapy with a qualified therapist." Do you see that?
A. Uh-huh.
Q. So as a requirement to receiving cross-sex hormones from your clinic, you actually require that the patient agree to continue psychotherapy with a qualified therapist, correct?
A. That's what it says right there.
Q. Well, and do you know that to be your actual practice?
A. It is our practice.
Q. Okay. Let's look at your expert report Page 31. And there you say in the final paragraph, "If my clinic is barred from providing this care, it is foreseeable and certain that transgender youth in Alabama will suffer medical

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and mental health consequences, including declining mental health, suicide ideation, suicide attempts, and possibly completed suicides." Do see that language?
A. I see that language.
Q. And if in your view it is foreseeable and certain that these negative effects will happen if you do not provide hormonal care for the puberty blockers, is it your professional opinion that these harms will be avoided if you are able to provide hormonal interventions?
A. These medical interventions are part of gender affirmation required by transgender, gender incongruent young people to live in accordance with their identified gender in a robust way. Will it -- we've talked about this today. Will it in a linear way prevent, we cannot say that. But we know that the inability to provide it will accelerate these negative effects.
Q. Well, on the proposition that it is certain that the absence of these treatments will cause worsening condition, you cite nothing. And

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part of what your expert report is to do is to provide us not only your opinions but the basis for those opinions. And I would like you to tell me what the basis of that opinion is.
A. There's a wealth of literature that comes together to underscore improved mental health, improved physical health for young people who are able to access this care. If this care is not available -- and I'm going to bifurcate that as well. Okay. Let's talk about youth who are gender incongruent who are at high risk for gender dysphoria and what comes with it who have no ability to receive this care. We know the outcomes will be lessened. Mental health alone has not been shown to alleviate some of the downstream serious negative effects of untreated gender dysphoria.
Q. Is it your testimony that studies which you believe to be a sufficiently large size and sound methodology have shown that hormonal interventions will alleviate these harms?
A. Alleviate is a strong word. Okay.
Q. I thought it was a weak word.

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A. Will mitigate.
Q. All right.
A. Okay. When, you know, taken together with all of the other factors, family support, et cetera. But the bifurcation that is also very very important in this statement is if my colleagues and I are forced to cease care for youth receiving it currently, okay, to just stop it, that's not only medically contraindicated, but it's an ethical breach, and it has been shown to be associated with these harms.
Q. That is ceasing care, ceasing hormonal care for those already receiving it has been shown?
A. Well, first of all, in the case -- in the unique case of testosterone, that's medically contraindicated regardless. Anyone receiving testosterone for any number of medical indications, including gender dysphoria. That's medication that medically you don't stop. It's medically contraindicated to just cease that, but.
Q. Let me ask you a question about that if I may.

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A. Okay.
Q. You've talked throughout the day about the fact or the possibility of the young people have a choice to cease cross-sex hormones if they choose to?
A. That's correct.
Q. Do you tell them before prescribing testosterone that it would be medically indicated not to stop it once they begin it?
A. We tell them and we talk at each visit that our patients have the freedom and ability to change their mind. In the unique case of testosterone, we tell them, we don't want you to simply stop the medication. But should you decide that taking the medication is not warranted for you, we will do this together under a medically supervised taper. We have yet to see this specific situation. But yes, we have those discussions.
Q. You referred earlier to children who were suffering gender incongruence and were at risk for gender dysphoria. Do you recall that?
A. I do.

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Q. Does your clinic prescribe either puberty blockers or cross-sex hormones for children who have not received a diagnosis of gender dysphoria?
A. We do not.
Q. Then what were you talking about when you talked about children who are gender incongruous and at risk for gender dysphoria if they don't receive treatment?
A. I was speaking of a group of young people who may be in the phase of developing or understanding a gender incongruent identity, meaning as it's evolving. Should they evolve into teens with a transgender identity and for many the accompanying dysphoria, to know that the standard of care medicine is not available to them could accelerate mental health -- negative mental health outcomes.
Q. Let me ask for your unbigoted testimony under oath as to whether your clinic ever provides puberty blockers or cross-sex hormones for any young person who has not received a formal diagnosis of gender dysphoria by a

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qualified mental health professional?
A. Are you asking: Is it conceivable the diagnosis could have been made by physician or others?
Q. Has your clinic ever prescribed puberty blockers or cross-sex hormones for a young person who has not received a formal diagnosis of gender dysphoria by an appropriately qualified medical or mental health provider?
A. No, sir.
Q. Okay.
A. We have not.
MR. BROOKS: Let me mark as Ladinsky Exhibit 31 a document entitled "Advancing knowledge of transgender medical intervention effects" by Joshua Safer, from the Urology Journal.

(Whereupon, Ladinsky Exhibit 31 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) Let me ask first

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whether you've ever had any professional interactions with Dr. Safer?
A. I have not.
Q. Do you -- have you heard of his professional reputation?
A. I have not.
Q. Are you familiar with the gender clinic at the Mount Sinai Medical Institute in Manhattan?
A. I know that they have one.
Q. Okay. But you had no interactions?
A. No, sir.
Q. Then this will be quick. Writing in 2019 in the very first paragraph, Dr. Safer says the following: When assessing the risks and benefits of transgender hormone therapy, the evidence base to guide decision-making is thin. Although transgender hormone treatment seems to be generally safe when prescribed under medical supervision, the data that exist are mostly from medical record review of convenience samples with dozens or hundreds of patients." And he goes on a little bit later in that same paragraph to say,

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quote, "The nature of these studies has been to show minimal harm rather than to show benefit." Do you see the language that I've read?

A. I'm sorry. I was reading the --

Q. Feel free to read the entire paragraph.

A. I was reading the sentence before that.

MS. EAGAN: Look through the whole document. You're not familiar with this document.

THE WITNESS: Not at all.

MS. EAGAN: Let's take time to --

Q. (BY MR. BROOKS) Let me ask a fairly simple question. If Dr. Safer concluded in 2019, November of 2019, that the studies available up to that point tended to show minimal harm rather than to show benefit from cross-sex hormone therapy for gender dysphoria, do you simply disagree with Dr. Safer?

A. I'm struggling with this because I -- my first glance is that Dr. Safer is commenting on an article that's similar to --

Q. That's correct. And up front he's

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summarizing the state of the science.

A. As he sees it.

Q. That's right. And my question for you is very simple. If, as he sees it, the state of the science is to show minimal harm rather than to show benefit from cross-sex hormones, do you simply disagree with his evaluation of the science?

A. I cannot in any way comment on Dr. Safer's impressions relative to this. This is a group -- the study involves and the analysis here involves a group of adults. These may well have been adults who transitioned as adults. Therefore, physiologically the changes they experienced from those hormones may be quite different than those experienced by an adolescent. In addition, it's tempered by their expectations, their perception of their own bodily feelings, pain, discomfort, or comfort. So that's what I'm seeing here if that helps.

Q. All right.

MR. BROOKS: Let me mark as Ladinsky Exhibit 32 a paper entitled "Psychological

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Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers" by authors including van der Miesen, Steensma, de Vries, and others with Dutch names. That's dated 2020.

(Whereupon, Ladinsky Exhibit 32 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) My first question to you, Dr. Ladinsky, will be whether this is an article that you have read before today?

A. I recall seeing this article. I cannot -- I don't recall detail.

MS. EAGAN: Take your time.

Q. (BY MR. BROOKS) I want to ask you not so much about the results but about a couple of cautions the authors authored. Page 703.

MS. EAGAN: Dr. Ladinsky, do you want to review the article?

Q. (BY MR. BROOKS) Well, let me ask the question before you review the whole article.

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If you turn to Page 703, an inch and a half from the bottom in the first column, maybe 2, is a sentence that reads, "It should be acknowledged that the care provided in the present study also involved the offering of appropriate mental health care." Period. Closed quote. Do you see that?

A. Hang on.

MS. EAGAN: What page?

MR. BROOKS: It's 703, the first column.

Q. And you're in the second column right now?

A. Okay.

Q. An inch and a half from the bottom of the first column.

A. Do you mind if I read the discussion quickly?

Q. Let me ask you a question first, and then you can decide what you need to read. What the authors here say is, "It should be acknowledged that the care provided in the present study also involved the offering of appropriate

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mental health care." Inch and half from the bottom of that column, maybe 2.
A. I got you.
Q. So let me ask: That's consistent with your clinic's practice where we saw you --
A. That's correct.
Q. -- require your patients to be receiving appropriate mental health care concurrently with whatever medical care you provide, correct?
A. That's correct. It is our practice.
Q. Does that -- just speaking general methodology, does that create what you early refer to as a confound when you attempt to analyze the significance of improvements or lack of improvements on the part of patients? I think you used the term. Do you understand what a confound is?
A. I do. I'm trying to put it into the context of what you're asking relative in addition to this.
Q. So let's put this study aside for a moment because just generally it studies gender

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dysphoric youths who are receiving medical intervention of some type?
A. Right.
Q. And you're measuring outcomes. If they are concurrently receiving mental healthcare, does that in your understanding create a confound that stands between you and formed conclusion about the effect of the medical care on the one hand versus the mental health care on the other?
A. No.
MS. EAGAN: Object.
Q. (BY MR. BROOKS) Why is that?
A. First of all, I'm not actively engaged in research. Are you insinuating, meaning when I'm evaluating --
Q. Exactly so.
A. -- successive treatment with an individual patient?
Q. Or when you're evaluating literature?
A. That's very different. Okay. When I'm evaluating literature as in this study?
Q. Or any study whether there's medical

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care and mental health care delivered concurrently?
A. In this -- in gender health, especially in work with adolescents, you know, to -- the mental health piece is standard of care for good reasons. I'm not a researcher, but I would not see it as a confounding variable because it's being received before, during, and ongoing, their receipt of these individual transitioning therapies. It shouldn't confound our analysis of success around the role of medication.
Q. Let me ask a question unrelated -- entirely unrelated to this paper. I don't think anything in the paper mentions this.
You testified that the large majority of your patients who come in are age 14 or above when you first see them, correct?
A. Many, yes.
Q. And is it the case that at least most young people who come to you at that stage in life are experiencing distress or mental health difficulties of one type or another?
A. Many.

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Q. And do you have any knowledge as to whether -- putting aside gender dysphoria in young people -- young people who are, let's say, at age 15 suffering mental health issues are on average in a better place, in the same place, or in a worse place two years later? In other words, does maturation in that age period, simple process of getting older, provide a statistical improvement in mental health?
A. I'm sorry. Were you talking about youth who experience gender dysphoria or the general population of just, say, cisgendered teenagers experiencing anxiety, depression?
Q. The latter.
A. The latter. Okay.
Q. My question is: Do you have any knowledge about whether such a trend either getting worse or getting better in that age period exists?
A. In my clinical experience as a primary care provider for children and adolescents, it is my experience that adolescents who have mental health challenges and are not

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provided therapeutic programming pharmacology around them, they do not get better. They can get far worse.

Q. Back to our friends at the Vrije University clinic in the second column of 703. The authors state 2 inches -- everything I call out is an inch or 2 from the bottom. So 2 inches from the bottom. The sentence that begins, "The present study can." Do you see that?

A. Got it.

Q. Let me read that in the record. "The present study can, therefore, not provide evidence about the direct benefits of puberty suppression over time and long-term mental health outcomes. Conclusions about long-term benefits of puberty suppression should thus be made with extreme caution needing prospective long-term follow-up studies with a repeated measure design with individuals being followed over time to confirm the current findings." Do you see that language?

A. I see that language.

Q. And do you agree that up to the

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present, conclusions about the long-term benefits -- this is what they specifically speak to -- of puberty suppression need to be made with extreme caution?

A. Without putting it into the context of the entire study, I don't know what they mean by "with extreme caution".

A clinical implication of these findings is the need for worldwide availability of gender-affirming care including puberty suppression to alleviate mental health problems.

MS. EAGAN: Dr. Ladinsky, you probably answered his question. He asked if you agree with that statement, and you said you can't do it without the context of the document. So I think it's time for another question.

MR. BROOKS: Well testified.

THE WITNESS: She's professional.

MR. BROOKS: Let me mark as Exhibit 33 a paper by Polly Carmichael dated 2021 entitled "Short-term outcomes of pubertal suppression in a selected cohort of 12-to-15-year-old young people with persistent gender dysphoria in the UK."

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(Whereupon, Ladinsky Exhibit 33 was marked and copy of same is attached hereto.)

Q. (BY MR. BROOKS) You'll see at a glance that this is research coming out of the Tavistock Clinic --

A. We do.

Q. -- that we spoke about earlier. Have you encountered professionally any of the authors of this article?

A. I have not.

Q. And is this article one that you believe that is part of your process of staying abreast of the literature in the field that you read sometime soon after it was published?

A. I vaguely recall it being published.

Q. They list in the methods paragraph certain metrics that they followed including youth self-report, CBCL, YSR. Are those metrics that you're familiar with?

A. The YSR, I'm not familiar with.

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I've heard of the CBCL. But these are, you know, as you see by the spelling of behavior, these are British tools.

Q. You know that to be the case? You don't believe that the CBCL and the YSR are used by American researchers as well?

A. They may well be used by American researchers as well, but I am not familiar with them, put it that way.

Q. And you see that this article is from February 2021. Do you see that?

A. It was published then, that's correct.

Q. Presumably the work done was earlier than that?

A. Yes, exactly.

Q. Do you recall -- you said you recall this being published. Obviously coming from a large and prestigious institute, correct?

A. The Tavistock/Portman Clinic is a very very well, you know, longstanding institutional source of care, yes.

Q. Was this, in your opinion, an

important piece of research information when it came out?

A. It was sort of an observational study looking at 44 young people receiving puberty blockers with persistent severe gender dysphoria. Their observations are always going to be of interest to anybody working in this field. Do I remember it as sentinel, I can't -- I don't recall.

MR. BROOKS: Well, with a minute or two to go, I will cede my time. I have no further questions for the witness.

MS. EAGAN: I do not have any questions.

COURT REPORTER: Do you want a copy of the transcript?

MS. EAGAN: Absolutely. We're going to read and sign.

(Whereupon, a discussion was held off the record.)

MR. BROOKS: The defendants are

withdrawing from the record Exhibit 2, which was as transcript of the May 5, 2022 session of the preliminary injunction hearing.

MS. EAGAN: And plaintiff is in agreement with that withdrawal, so it will not part of this deposition transcript.

(Whereupon, the deposition ended at 5:56 p.m.)

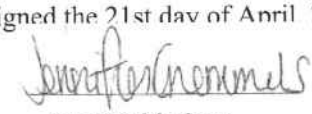
CERTIFICATE

STATE OF ALABAMA)
JEFFERSON COUNTY)

I hereby certify that the above and foregoing proceeding was taken down by me in stenotype, and the questions and answers thereto were transcribed by means of computer-aided transcription, and that the foregoing represents a true and correct transcript of the testimony given by said witness upon said hearing.

I further certify that I am neither of counsel, nor of kin to the parties to the action, nor am I in anyway interested in the result of said cause.

Signed the 21st day of April 2023.



Jennifer Madaris
ACCR 585
My license expires September 30, 2023
My Commission expires January 4, 2026

To: Melody H. Eagan, Esq.
Re: Signature of Deponent Morissa J. Ladinsky, M.D.
Date Errata due back at our offices: 30 days

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I, the undersigned, do hereby certify that I have read the transcript of my testimony, and that

___ There are no changes noted.

___ The following changes are noted:

Pursuant to Civil Procedure, Rule 30. ALA. CODE § 5-30(e) (2017). Rule 30(e) states any changes in form or substance which you desire to make to your testimony shall be entered upon the deposition with a statement of the reasons given for making them. To assist you in making any such corrections, please use the form below. If additional pages are necessary, please furnish same and attach.

Page _____ Line _____ Change _____

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Reason for change _____

Page _____ Line _____ Change _____

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Reason for change _____

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DEPONENT'S SIGNATURE

Sworn to and subscribed before me this ___ day of

_____, _____.

_____

NOTARY PUBLIC / My Commission Expires:_____

EXHIBIT 65

Patient Information for Informed Consent
FEMINIZING MEDICATIONS FOR TRANSGENDER CLIENTS
Minors and Parents/Guardians
University of Alabama at Birmingham Pediatric Endocrinology
Multidisciplinary Gender Health Team

Before using medications to transition and feminize, you and your parents or guardians need to know the possible advantages, disadvantages and risks of these medications. We have listed them here for you. It's important that you understand all of this information before you begin taking these medications.

Please read the following with your parent or guardian. Once your questions or concerns are addressed, and you have decided to proceed with the medication(s), both you and your parent or guardian will need to sign this information and consent form.

We are happy to answer any questions you have.

What are the different medications that can feminize my appearance?

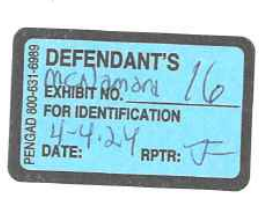
Part of transition for many transgender people involves taking hormones. For hormone treatment to be most effective, transgender girls and women take not only estrogens (female hormones), but also medicines to block their body from producing or utilizing testosterone (male hormones).

Different forms of the hormone estrogen are used to feminize appearance in transgender females. Estrogen can be given as an injection, weekly or every other week, as a pill, daily or twice a day, or as a patch, which is changed every three or four days.

Medications that block the production or effects of testosterone are called androgen blockers. Androgen is another term for male sex hormones. Spironolactone is the androgen blocker that is most commonly used in the United States. Other medicines are sometimes used, but because spironolactone is relatively safe, inexpensive, and effective to block testosterone, it is the primary androgen blocker used for transgender women.

Every medication has risks, benefits, and side effects that are important to understand before starting. The effects and side effects of medicines used for transition need to be monitored with laboratory studies and regular visits to your provider to make sure that there are no negative effects on your body.

Both the medicines that you take, as well as the process of transitioning can affect your mood. While trans women are relieved and happy with the changes that occur, it is important that you are under the care of a gender-qualified therapist while undergoing transition. The therapist can work with you, your family and friends and your school staff.



Estrogen can cause blood clots. We must be careful that you are not at risk to develop a blood clot. Who should not take estrogen?

Estrogen should not be used by anyone who has a history of

- an estrogen-dependent cancer
- a disorder that makes them more likely to get blood clots that could travel to the lungs (unless they are also taking blood thinners and are followed by a specialist)

Estrogen should be used with caution and only after a full discussion of risks by anyone who

- has a strong family history of breast cancer or other cancers that grow quicker when estrogens are present
- has uncontrolled diabetes
- has heart disease
- has chronic hepatitis or other liver disease
- has uncontrolled high cholesterol
- has migraines or seizure
- is obese
- smokes cigarettes

Both you and your parent or guardian should initial and date each statement on this form to show that you and your parent or guardian understand the benefits, risks, and changes that may occur from taking these medications.

Effects of Feminizing Medications

_____ _____I know that estrogen or anti-androgens – or both – may be prescribed to feminize my appearance.

_____ _____I know it can take several months or longer for the effects to become noticeable. I know that no one can predict how fast – or how much – change will happen.

_____ _____I know that if I am taking estrogen I will develop breasts.

- I know it takes several years for breasts to get to their full size.
- I know the breasts will remain, even if I stop taking estrogen.
- I know I might have a milky discharge from my nipples (called galactorrhea). If I do, I know I should check it out with my healthcare provider because it could be caused by the estrogen or by something else.
- I know that while we do not know the exact risk the risk, my risk of breast cancer may be increased to as high as if I had been born female
- I know that I should take care of my breasts like every other woman. This includes annual breast exams from my health provider, and when I am older, regular mammograms.

_____ _____I know that the following changes are usually not permanent — they are likely to go away if I stop taking the medicines.

- I know my body hair will become less noticeable and will grow more slowly. But it won't stop completely, even if I take the medicines for years.
- I know I will probably have less fat on my abdomen and more on my buttocks, hips, and thighs. It will be redistributed to a more female shape — changing from "apple" shape to "pear" shape.
- I know that if I have the predisposition to have male pattern baldness it may start later than it would have, but may not stop completely.
- If I stop taking hormones I may lose my hair faster than if I hadn't taken hormones.
- I know I may lose muscle and strength in my upper body.
- I know that my skin may become softer.

_____ _____I know that my body will make less testosterone (an androgen, or male hormone). This may affect my sex life in different ways and future ability to cause a pregnancy:

- I know my sperm may no longer get to full maturity. This could make me less able to cause a pregnancy. I also know that there is a small risk that I might never produce mature sperm again. But I know that it's also possible that my sperm could still mature even while I am taking hormones. So, I know that I might get someone pregnant if we have vaginal intercourse and we don't use birth control.
- The options for sperm banking have been explained to me.
- I know that my testicles may shrink down to half their size. Even so, I know that they are part of my body and that I need to take care of them unless I have surgery to remove them. This means that I will need regular checkups for them.
- I know that I won't have as much semen when I ejaculate.
- I know it is likely that I won't have erections upon waking as often as before, and it is likely that I will have fewer spontaneous erections.
- I know I may not be able to achieve or maintain an erection for penetrative sex.
- I know that I may want to masturbate less or have sex less, and may find it harder to ejaculate when I do.
- I know this treatment may (but is not assured to) make me permanently unable to make a woman pregnant.

_____ _____I know that some parts of my body will not change much by using these medicines.

- I know the hair of my beard and mustache may grow more slowly than before. It may become less noticeable, but it will not go away unless I have treatments like electrolysis.
- I know the pitch of my voice will not rise, and my speech patterns will not become more like a woman's.
- I know my Adam's apple (called the laryngeal prominence) will not shrink.
- Although these medicines can't make these changes happen, there are other treatments that may be helpful.

_____ _____ I know that there may be mood changes with these medicines. I agree to continue therapy with a qualified therapist.

_____ _____I know if I have any concerns about these issues, you can make referrals for me to help me explore other treatment options.

Risks of Feminizing Medications

_____ _____I know that the side effects and safety of these medicines are not completely known. There may be long-term risks that are not yet known.

_____ _____I know not to take more medicine than I am prescribed. I know it increases health risks. I know that taking more than I am prescribed won't make changes happen more quickly or more significantly.

_____ _____ I know these medicines may damage the liver and may lead to lead to liver disease. I know I should be checked for possible liver damage as long as I take them.

_____ _____I know these medicines cause changes that other people will notice. Some transgender people have experienced discrimination because of this. I know my clinician can help me find advocacy and support resources.

Risks of Estrogen

_____ _____I know that taking estrogen increases the risk of blood clots or problems with blood vessels that can result in

- chronic problems with veins in the legs
- heart attack
- pulmonary embolism – blood clot to the lungs – which may cause permanent lung damage or death
- stroke, which may cause permanent brain damage or death

_____ _____I know that the risk of blood clots is much worse if I smoke cigarettes. I know the danger is so high that I should stop smoking completely if I start taking estrogen. I know that I can ask my clinician for advice about how to stop smoking.

_____ _____ I know taking estrogen can increase the deposits of fat around my internal organs. This can increase my risk for diabetes and heart disease.

_____ _____I know taking estrogen can raise my blood pressure. I know that if it goes up, my clinician can work with me to try to control it with diet, lifestyle changes, and/or medication.

_____ _____I know that taking estrogen increases my risk of getting gallstones. I know I should talk with my clinician if I get severe or long-lasting pain in my abdomen.

_____ _____I know that estrogen can cause nausea and vomiting. I know I should talk with my clinician if I have long-lasting nausea or vomiting.

_____ _____I know that estrogen can cause migraines or make them worse if I already have them. I know I should talk with my clinician if I have headaches or migraines often or if the pain is unusually severe.

_____ _____I know that it is not yet known if taking estrogen increases the risk of prolactinomas. These are non-cancerous tumors of the pituitary gland. I know they are not

usually life threatening, but they can damage vision and cause headaches if they are not treated properly. I know that changes in vision, headaches that are worse when I wake up in the morning, and milky discharge from my nipples can be signs of a prolactinoma, and I should talk to my health care provider if I develop these symptoms. There is a blood test that can check for this.

_____ _____I know that I am more likely to have dangerous side effects if

- I smoke.
- I am overweight.
- I have a personal or family history of blood clots.
- I have a personal or family history of heart disease and stroke.
- My family has a history of breast cancer.

Risks of Androgen Antagonists (Spironolactone)

_____ _____I know that spironolactone affects the balance of water and salts in the kidneys. This may

- Increase the amount of urine I produce, making it necessary to urinate more frequently.
- Increase thirst.
- Rarely, cause high levels of potassium in the blood, which can cause changes in heart rhythms that may be life-threatening.
- Reduce blood pressure.

_____ _____I know some androgen antagonists make it more difficult to evaluate test results for cancer of the prostate. This can make it more difficult to check up on prostate problems. I know that if I am over 50, I should discuss appropriate prostate cancer screening with my care provider. I know that even if I have genital sex reassignment surgery the prostate is not usually removed.

Prevention of Medical Complications

_____ _____I agree to take feminizing medications as prescribed. And I agree to tell my care provider if I have any problems or am unhappy with the treatment.

_____ _____I know that the dose and type of medication that's prescribed for me may not be the same as someone else's.

_____ _____I know I need periodic physical exams and blood tests to check for any side effects.

_____ _____I know that in addition to periodic checks from my provider, I must also treat my body with respect. This means that paying attention and talking to my provider if I develop any symptoms that might be side effects from medicines. This also means keeping my partners and myself safe, when and if I choose to have sex with others, by using condoms or methods to keep me safe from sexually transmitted infections (STIs).

_____ _____I know that feminization medications can interact with other drugs and prescribed and over the counter medicines. These include alcohol, diet supplements, herbs, other hormones, and street drugs. This kind of interaction can cause dangerous complications. I know that I need to prevent complications because they can be life threatening. That's why I need to be honest with my provider about whatever else I take. I also know that I will continue to get medical care here no matter what I share about what I take.

_____ _____I know that it can be risky for anyone with certain conditions to take these medicines. I agree to be evaluated if my clinician thinks I may have one of them. Then we will decide if it's a good idea for me to start or continue using them.

_____ _____I know that I should stop taking estrogen two weeks before any surgery or when I may be immobile for a long time (for example, if I break my leg and am in a cast). This will lower the risk of getting blood clots. I know I can start taking it again a week after I'm back to normal or when my clinician says it's okay.

_____ _____ I know that even if I have to stop my estrogens, I may still be able to take the testosterone blockers that I am on, to help prevent the effects of my testicles producing testosterone again.

_____ _____I know that using these medicines to feminize is an off-label use. I know this means it is not approved by the Food and Drug Administration (FDA). I know that the medicine and dose that is recommended for me is based on the judgment and experience of my health care provider and the best information that is currently available in the medical literature.

_____ _____I know that I can choose to stop taking these medicines at any time. I know that if I decide to do that, I should do it with the help of my clinician. This will help me make sure there are no negative reactions. I also know my clinician may suggest that I cut the dose or stop taking it at all if certain conditions develop. This may happen if the side effects are severe or there are health risks that can't be controlled.

Alternatives

There are alternatives to using feminizing medicines to help people appear more feminine. Some transgender people choose to not take hormones or have surgery and may only socially transition. If you are interested in alternatives, talk with your health care provider about your options.

Our signatures below confirm that

- My clinician has talked with me and my parents or guardian about
  - the benefits and risks of taking feminizing medication
  - the possible or likely consequences of hormone therapy
  - potential alternative treatments
- I understand the risks that may be involved.
- I know that the information in this form includes the known effects and risks. I also know that there may be unknown long-term effects of risks.
- I have had enough opportunity to discuss treatment options with my clinician.
- All of my questions have been answered to my satisfaction.
- I believe I know enough to give informed consent to take, refuse, or postpone therapy with feminizing medications.

Based on all this information

_____ I want to begin taking estrogen.

_____ I want to begin taking androgen antagonists (e.g., spironolactone).

_____ I do not wish to begin taking feminizing medication at this time.

_____ _____
Patient Signature Date

_____ _____
Signature of Parent or Guardian Date

_____ _____
Prescribing clinician signature Date

Your health is important to us. If you have any questions or concerns please call us at (205) 638 9107. We are happy to help you.

Client Information for Informed Consent

TESTOSTERONE FOR TRANSGENDER CLIENTS
Minors and Parents/Guardians
University of Alabama at Birmingham Pediatric Endocrinology
Multidisciplinary Gender Health Team

Before using testosterone to transition and masculinize your body, you and your parents or guardians need to know the possible advantages, disadvantages and risks of these medications. We have listed them here for you. It's important that you understand all of this information before you begin taking these medications.

Please read the following with your parent or guardian. Once your questions or concerns are addressed, and you have decided to proceed with the medication(s), both you and your parent or guardian will need to sign this information and consent form.

We are happy to answer any questions you have.

What is testosterone?

It is the sex hormone that makes certain features appear typically male. It builds muscle and causes the development of facial hair and a deeper voice.

How is testosterone taken?

It is usually injected every one to four weeks. It is not used as a pill because the body may not absorb it properly and may cause potentially fatal liver problems. Some people use skin creams and patches, but they tend to be more expensive and aren't recommended for initiating puberty or for use in teenagers and young adults.

The doses used for injection differ from product to product and from patient to patient. They may range from 50 to 400mg. The injections are given in a large muscle to slow the release of the hormone. You may experience unwanted swings in hormone levels. You may control the swings by changing how often the dose is given and how much of a dose is given.

Every medication has risks, benefits, and side effects that are important to understand before starting. The effects and side effects of medicines used for transition need to be monitored with laboratory studies and regular visits to your provider to make sure that there are no negative effects on your body.

The medicines that you take, as well as the process of transitioning can affect your mood. While trans men are usually relieved and happy with the changes that occur, it is important that you are under the care of a gender-qualified therapist while undergoing transition. The therapist can work with you, your family and friends and your school staff.

Warning — Who should not take testosterone?

It should *not* be used by anyone who is pregnant or has uncontrolled coronary artery disease as it could increase your risk for a fatal heart attack:

It should be used with caution and only after a full discussion of risks by anyone who

- Has acne
- Has a family history of heart disease or breast cancer
- Has had a blood clot
- Has high levels of cholesterol
- Has liver disease
- Has a high red-blood-cell count
- Is obese
- Smokes cigarettes

Periodic blood tests to check on the effects of the hormone will be needed. Routine breast exams and pelvic exams with Pap tests should be continued, when applicable.

Summary of Testosterone Benefits and Risks

BENEFITS	RISKS

• Appearing more like a man
  ○ Bigger clitoris
  ○ Coarser skin
  ○ Lower voice
  ○ More body hair
  ○ More facial hair
  ○ More muscle mass
  ○ More strength
  ○ No more menstrual periods
• More physical energy
• More sex drive
• Protection against bone thinning (osteoporosis)
	• Acne (may permanently scar)
	• Blood clots (thrombophlebitis), risk significantly increased by smoking
	• Emotional changes, for example, more aggression
	• Headache
	• High blood pressure (hypertension)
	• Increased red-blood-cell count
	• Infertility
	• Inflamed liver
	• Interaction with drugs for diabetes and blood thinning — for example Coumadin and Warfarin
	• Male pattern baldness
	• More abdominal fat — redistributed to a male shape
	• More risk of heart disease
	• Swelling of hands, feet, and legs
	• Weight gain

Both you and your parent or guardian should initial and date each statement on this form to show that you and your parent or guardian understand the benefits, risks, and changes that may occur from taking this medications.

2

Masculinizing

_____I know that testosterone may be prescribed to make me appear less like a woman and more like a man.

_____ I know it can take several months or longer for the effects to become noticeable. I know that no one can predict how fast – or how much – change will happen. I know that the changes may not be complete for two to five years after I start.

_____I know that the following changes are likely and permanent even if I stop taking testosterone:

- Bigger clitoris — typically about half an inch to a little more than an inch
- Deeper voice
- Gradual growth of mustache and beard
- Hair loss at the temples and crown of the head — possibility of being completely bald
- More, thicker, and coarser hairs on abdomen, arms, back, chest, and legs

_____ I know that the following changes are usually not permanent — they are likely to go away if I stop taking testosterone:

- Acne (although there may be permanent scars)
- Menstrual periods typically stop one to six months after starting
- More abdominal fat – redistributed to a male shape: decreased on buttocks, hips, and thighs; increased in abdomen – changing from "pear shape" to "apple shape"
- More muscle mass and strength
- More sex drive
- Vaginal dryness

_____I know that the effects of testosterone on fertility are unknown. I have been told that I may or may not be able to get pregnant even if I stop taking testosterone. I know that I might still get pregnant even after testosterone stops my menstrual periods. I know about my birth control options (if applicable). And I know that I can't take testosterone if I am pregnant and that I must take a pregnancy test prior to starting testosterone therapy.

_____ I know that some aspects of my body will not be changed:

- Losing some fat may make my breasts appear slightly smaller, but they will not shrink very much.
- My voice will deepen, but other aspects of the way I speak may not sound more masculine.
- Although testosterone can't make these changes happen, there are other treatments that may be helpful.

_____I know that there may be mood changes with these medicines. I agree to continue therapy with a qualified therapist.

_____I know if I have any concerns about these issues, you can make referrals for me to help me explore other treatment options.

Risks of Testosterone

_____I know the medical effects and the safety of testosterone are not completely known. There may be long-term risks that are not yet known.

_____I know not to take more testosterone than prescribed. Taking too much:

- Will increase health risks
- Won't make changes happen more quickly or more significantly
- Can cause my body to convert extra testosterone into estrogen, and that can slow down or stop my appearing more masculine

_____I know that testosterone can cause changes that increase my risk of heart disease. These changes include having:

- Less good cholesterol (HDL) that may protect against heart disease and more bad cholesterol (LDL) that may increase the risk of heart disease
- Higher blood pressure
- More deposits of fat around my internal organs

_____I know that my risk of heart disease is higher if people in my family have had heart disease, if I am overweight, or if I smoke.

_____I know that I should have periodic heart-health checkups for as long as I take testosterone. This means I must watch my weight and cholesterol levels and have them checked by my clinician.

_____I know testosterone can damage the liver and possibly lead to liver disease and I should be checked for possible liver damage for as long as I take testosterone.

_____I know testosterone can increase my red blood cells and hemoglobin. This increase is usually only to what is normal for a man and shouldn't cause any health risks. However, there is a small possibility that higher levels of red blood cells and hemoglobin may increase my risk of life-threatening problems such as stroke or heart attack. That's why I know I need to have periodic blood checks for as long as I take testosterone.

_____I know that taking testosterone can increase my risk for diabetes. It may decrease my body's response to insulin, cause weight gain, and increase deposits of fat around my internal organs. Therefore, I should have periodic checks of my blood glucose for as long as I take testosterone.

_____I know my body can turn testosterone into estrogen and that no one knows if that could increase the risk of cancers of the breast, the ovaries, or the uterus.

_____I know taking testosterone can thin the tissue of my cervix and the walls of my vagina. This can lead to tears or abrasions during vaginal sex or play with a male or female partner. These tears increase my risk of getting a sexually transmitted infection, including HIV. I know I should speak frankly with my primary care provider about my sex life to learn the best ways to prevent and check for infections.

_____I know that testosterone can give me headaches or migraines. I know that it's best to talk with my clinician if I get them a lot or if the pain is unusually severe.

_____I know that testosterone can cause emotional changes. For example, I could become more irritable, frustrated, or angry. I know that my clinician can help me find resources to explore and cope with these changes.

_____I know that testosterone causes changes that other people will notice. Some transgender people have experienced harassment, discrimination, and violence because of this. Others have lost the support of loved ones. I know my clinician can help me find advocacy and support resources.

Prevention of Medical Complications

_____I agree to take testosterone as prescribed. I agree to not purchase testosterone or other hormones without my physician's knowledge, and I agree to tell my clinician if I have any problems or am unhappy with the treatment.

_____I know that the dose and type of medication that's prescribed for me may not be the same as someone else's.

_____I understand that the medications prescribed are for my use only and I will not supply these medications to others.

_____I know I need periodic physical exams and blood tests to check for any side effects.

_____I know testosterone can interact with other drugs and medicines. These include alcohol, diet supplements, herbs, other hormones, and street drugs. This kind of interaction can cause complications. I know that I need to prevent complications because they can be life-threatening. That's why I need to be honest with my clinician about whatever else I take. I also know that I will continue to get medical care here no matter what I share about what I take.

_____ _____ I know that it can be risky for anyone with certain conditions to take testosterone. I agree to be evaluated if my clinician thinks I may have one of them. Then we will decide if it's a good idea to start or continue using testosterone.

_____ _____ I know that using testosterone to masculinize is an off-label use. This means it is not approved by the Food and Drug Administration (FDA). I know that the medicine and dose that is recommended for me is based on the judgment and experience of my health care provider and the best information that is currently available in the medical literature.

_____ _____ I understand that my insurance company may not cover the costs of this treatment. If so, I accept responsibility for any charges associated with this treatment. Costs of treatment can be obtained by contacting The Pediatric Endocrinology office at 205 638 9107.

_____I know that I can choose to stop taking testosterone at any time. I know that if I decide to do that, I should do it with the help of my clinician. This will help me make sure there are no negative reactions. I also know my clinician may suggest that I cut the dose or stop taking it at all if certain conditions develop. This may happen if the side effects are severe or there are health risks that can't be controlled.

Alternatives

There are alternatives to using testosterone to help people appear more masculine. Some transgender people choose to not take hormones or have surgery and may only socially transition. If you are interested in alternatives, talk with your health care provider about your options.

Our signatures below confirm that:

- My clinician has talked with me and my parents or guardians about
  - The benefits and risks of taking testosterone
  - The possible or likely consequences of hormone therapy
  - Potential alternative treatments
- I understand the risks that may be involved.
- I know that the information in this form includes the known effects and risks. I also know that there may be unknown long-term effects of risks.
- I have had enough opportunity to discuss treatment options with my clinician.
- All of my questions have been answered to my satisfaction.
- I believe I know enough to give informed consent to take, refuse, or postpone testosterone therapy.

Based on all this information:

_____I want to begin taking testosterone.

_____I do not wish to begin taking testosterone at this time.

_____ _____
Patient Signature Date

_____ _____
Signature of Parent or Guardian Date

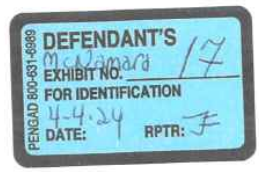
_____ _____
Prescribing Clinician Signature Date

Your health is important to us. If you have any questions or concerns please call us at (205) 638 9107. We are always happy to help you.

7

Original Research

Transgender Men Who Experienced Pregnancy After Female-to-Male Gender Transitioning



Alexis D. Light, MD, MPH, Juno Obedin-Maliver, MD, MPH, Jae M. Sevelius, PhD, and Jennifer L. Kerns, MD, MPH

OBJECTIVE: To conduct a cross-sectional study of transgender men who had been pregnant and delivered after transitioning from female-to-male gender to help guide practice and further investigation.

MATERIALS AND METHODS: We administered a web-based survey from March to December 2013 to inquire about demographics, hormone use, fertility, pregnancy experience, and birth outcomes. Participants were not required to have been on hormone therapy to be eligible. We used a mixed-methods approach to evaluate the quantitative and qualitative data.

RESULTS: Forty-one self-described transgender men completed the survey. Before pregnancy, 61% (n=25) had used testosterone. Mean age at conception was 28 years with a standard deviation of 6.8 years. Eighty-eight percent of oocytes (n=36) came from participants' own ovaries. Half of the participants received prenatal care from a physician and 78% delivered in a hospital. Qualitative themes included low levels of health care provider awareness and knowledge about the unique needs of pregnant transgender men as well as a desire for resources to support transgender men through their pregnancy.

CONCLUSION: Transgender men are achieving pregnancy after having socially, medically, or both transitioned. Themes from this study can be used to develop transgender-appropriate services and interventions that may improve the health and health care experiences of transgender men.

(Obstet Gynecol 2014;124:1120–7)
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Transgender individuals often report many barriers in attempting to access health care.[1] The American College of Obstetricians and Gynecologists (the College) recently called on obstetrician–gynecologists to help eliminate these barriers for transgender men (also called female-to-male individuals) by creating nondiscriminatory practices, assisting with gender transition, and providing transgender-appropriate and comprehensive health care.[2] Despite the College's call to action, little systematic attention has been paid to the health and reproductive experiences of transgender men or those individuals who are born with female sexual organs but who identify as male.

Transgender men are individuals who have a male or masculine gender identity but were assigned female at birth. The gender affirmation process may include social, medical, and surgical aspects of transition, although not all transgender men desire medical intervention.[3] Many transgender men desire children[4] and there are anecdotal reports supporting the biological possibility of pregnancy for transgender men who retain a uterus and discontinue testosterone therapy.[5–7] However, there is little scientific literature describing pregnancy experiences among transgender men or the effects of exogenous administration of testosterone on fertility, pregnancy, and neonatal outcomes.[8] Understanding transgender men's experiences with fertility, pregnancy, and birth will allow health care providers to augment pre- and posttransition discussions regarding fertility options, the roles of cross-sex hormones on fecundity, potential birth outcomes, and to support their physical and mental well-being during pregnancy. Expanded knowledge may also help

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health care providers support transgender men in attaining and maintaining healthy pregnancies.

We conducted a mixed-methods study to explore the experiences of transgender men and to contribute to the knowledge base of fertility, conception, pregnancy experience, and birth outcomes among transgender men.

MATERIALS AND METHODS

We conducted a cross-sectional survey from March to December 2013 of transgender men (assigned female at birth with a masculine, transmasculine, transmale, or female-to-male gender identity) who had been pregnant and delivered a neonate. Inclusion criteria were: age older than 18 years, self-identification as male before pregnancy, pregnancy within the last 10 years, and the ability to fill out the survey in English. Eligibility criteria did not require any type of medical (eg, testosterone use) or surgical (eg, bilateral mastectomy) transition. We recruited study participants through convenience sampling and we collected data using a web-based survey. Participation was not limited by geographic location.

We administered the online survey through REDCap,[9] an encrypted and secure online survey platform. The study contained 47 multiple-choice questions and 24 questions addressing demographics, hormone use, fertility, pregnancy experience, birth experience, and fetal outcomes. The survey concluded with four open-ended questions: "Is there anything you would like medical providers to know about transgender men and pregnancy?" "What was the experience of being pregnant like for you?" "What was the experience of giving birth like for you?" "What was the postpartum experience like for you?" The survey was developed by the authors in consultation with the Center of Excellence for Transgender Health at University of California, San Francisco and other health care providers serving the transgender community.

Initial recruitment occurred through distribution to key stakeholders in lesbian, gay, bisexual, and transgender health centers; transgender community groups; and Internet-based social networking pages created by study authors. We recruited additional participants through initial contacts. We provided interested individuals with a comprehensive study description and links to the study. After accessing the electronic study web site, participants were presented with informed consent documents and participants confirmed their consent through accessing a link to web-based survey. No in-person contact was made with survey participants.

We conducted a mixed-methods analysis to evaluate the quantitative and qualitative data collected from the survey. Using STATA 13.0, we performed unadjusted analyses using χ^2 for method of delivery; *t* tests for pregnancy age, body mass index, and gestational age; and Fisher's exact for all other variables according to testosterone use before pregnancy. As a result of nonresponse, variable totals may not sum to column totals or within category totals. A *P* value of $\leq .05$ was considered statistically significant. We analyzed the qualitative data using grounded theory, identifying iterative themes, and adding new codes as concepts emerged.[10] This study was approved by the University of California, San Francisco Committee on Human Research.

RESULTS

We excluded nine of the 56 participants who began the survey as a result of insufficient responses for analysis, and six others were excluded because they did not meet study criteria indicating male gender before pregnancy.[11] We included participants who identified as female or preferred "she" or "her" pronouns only if they had more than one validating indicator of a transgender identity (use of testosterone, male identity with female pronouns, or female identity with male pronouns). Forty-one participants remained for final analysis (Table 1). Most of our participants were from the western United States, identified as white, and had completed at least some college. Pronoun preference differed between those who had used testosterone and those who had not ($P=.04$). Participants who had previously used testosterone were more likely to prefer the pronoun "he," whereas those who had not used testosterone were more likely to identify with "they." Although most respondents were primiparous, those who had not used testosterone were more likely to be multiparous ($P=.006$). Four transgender men (10%), all of whom had been on testosterone previously, reported a prior diagnosis of polycystic ovary syndrome.

Twenty-five (61%) transgender men reported using testosterone before pregnancy (Table 2). Among those who had used testosterone, 20 (80%) reported resuming menstruation within 6 months after stopping testosterone. Five participants (20%) conceived while still amenorrheic from testosterone use. After pregnancy, six (38%) participants who had not previously used testosterone before pregnancy initiated use. Ten participants (40%) who had been on previously testosterone reported that they had not yet resumed testosterone use after pregnancy.

Table 1. Participant Characteristics

Characteristic	All (N=41)	Prior Testosterone Use		P
		Yes (n=25)	No (n=16)	
Age (y)*	28±6.8	29±6.9	27±6.8	.5
Gender identity†				.07
Male	21 (51)	12 (48)	9 (56)	
Transgender, female-to-male, transman	10 (24)	9 (36)	1 (6)	
Bigender, gender fluid, genderqueer	8 (20)	3 (12)	5 (31)	
Female	1 (2)	1 (4)	0	
Other	1 (2)	0	1 (6)	
Personal pronoun preference‡				.04
He	32 (82)	21 (88)	11 (73)	
They	3 (8)	0	3 (20)	
She	2 (5)	2 (8)	0	
Ey	1 (2)	1 (4)	0	
No pronouns	1 (2)	0	1 (7)	
Country				.4
United States	35 (85)	20 (80)	15 (94)	
Outside United States§	6 (15)	5 (20)	1 (6)	
U.S. region‡‖				.9
West	19 (59)	11 (61)	8 (57)	
Northeast	5 (16)	3 (17)	2 (14)	
South	5 (16)	2 (11)	3 (21)	
Midwest	3 (9)	2 (11)	1 (7)	
Race or ethnicity‡				1.0
White	36 (92)	21 (88)	15 (100)	
Asian	1 (3)	1 (4)	0	
Asian and black	1 (3)	1 (4)	0	
Native Hawaiian or other Pacific Islander	1 (3)	1 (4)	0	
Education level‡				.7
High school degree or less	4 (10)	3 (12.5)	1 (7)	
Vocational training or some college	12 (31)	6 (25)	6 (40)	
Associate or Bachelor's degree	14 (36)	10 (42)	4 (27)	
Master's or doctoral degree	9 (23)	5 (21)	4 (27)	
Annual household income ($)‡				.4
Less than 20,000	6 (15)	2 (8)	4 (25)	
20,000–59,999	20 (49)	12 (50)	8 (50)	
60,000–100,000	8 (20)	6 (25)	2 (13)	
More than 100,000	5 (13)	4 (17)	1 (7)	
Multiparous (2 or more pregnancies)	15 (37)	5 (20)	10 (63)	.006
Previous PCOS diagnosis	4 (10)	4 (16)	0	.15
BMI at the start of pregnancy (kg/m^2)	26±6	26±6	27±6	.6
Gender-confirming surgical procedure‡¶				.7
Bilateral mastectomy	19 (46)	13 (52)	6 (38)	
Oophorectomy	2 (5)	0	2 (13)	
Hysterectomy	2 (5)	2 (8)	0	
Phalloplasty or metoidioplasty#	1 (2)	1 (4)	0	

PCOS, polycystic ovary syndrome/BMI, body mass index.
Data are mean±standard deviation or n (%) unless otherwise specified.
* Age at the beginning of their most recent pregnancy.
† Kuper et al.[28]
‡ Not all the participants answered this question.
§ Canada (n=2), Germany (n=1), England (n=1), Israel (n=1), and Switzerland (n=1).
‖ Regions were defined according to the 2010 U.S. census.
¶ Surgery may have occurred before or after pregnancy.
# Metoidioplasty is procedure that separates the clitoris from the labia to assume a physiologic position similar to a penis (Djordjevic et al[29]).

Two thirds of pregnancies were planned (Table 3). Before the most recent pregnancy, condoms were the most common form of contraception followed by no form of contraception and abstinence (defined as not engaging in penile–vaginal intercourse). Those who had previously used testosterone were more likely to

Table 2. Findings Among Those Who Used Testosterone Before Pregnancy of Report (n=25)

Characteristic	Value
Age (y) when testosterone was initiated	25 (17–35)
Length of testosterone use before pregnancy (y)	
Less than 1	10 (40)
1–2	6 (24)
3–10	4 (16)
More than 10	5 (20)
Stopped taking testosterone to become pregnant	17 (68)
Duration between stopping testosterone and resumption of menses (mo)	
No menses before pregnancy	5 (20)
Less than 1	2 (8)
1	6 (24)
2	7 (28)
3	4 (16)
4–6	1 (4)
Resumed or initiated testosterone after pregnancy*	20 (48)

Data are median (range) or n (%).
* Of total respondents in the study (N=41).

report no contraceptive use or abstinence, whereas those who had not used testosterone were more likely to use a hormonal contraceptive method (P=.03). The majority of oocytes came from the participants' own ovaries, whereas the majority of sperm came from a significant other or spouse. Most transgender men became pregnant within 4 months of trying, only 15% had a preconception medical consultation, and 7% used fertility drugs to become pregnant.

Pregnancy, delivery, and birth outcomes did not differ according to prior testosterone use (Table 4). Half of the participants received prenatal care from a physician, 40% from an obstetrician, and 10% from a family medicine physician. More than three fourths of the participants began taking prenatal vitamins either before pregnancy or within the first trimester, whereas 15% reported not taking any prenatal vitamins. Participants reported a variety of perinatal complications including hypertension (12%), preterm labor (10%), placental abruption (10%), and anemia (7%). Anemia was not reported by participants who had previously used testosterone. A higher proportion of transgender men who had used testosterone underwent cesarean delivery compared with those who reported no testosterone use (36% compared with 19%, respectively), although this finding was not statistically significant. Among those who underwent a cesarean delivery, 25% cited the indication as elective. Those who had previously used testosterone were statistically less likely to chest (breast) feed their infant than those who had not previously used testosterone (P=.04).

Thirty participants (73%) answered at least one of the four open-ended questions. Major themes from these responses were: 1) effect of pregnancy on concepts of family structure; 2) isolation; 3) gender dysphoria and pregnancy; and 4) interactions with health care providers.

Many participants discussed their pregnancy in the context of family structure. For some, pregnancy was a necessary step in creating the family they desired: "I looked at it as something to endure to have a child" (36-year-old, prior testosterone use). Others described the pregnancy in pragmatic terms, possibly as a way to avoid gender dissonance: "Like my body was a workshop, building up this little kid" (35-year-old, prior testosterone use). Another participant found a way to embrace the pregnancy, describing the pregnancy and birth as a bridge to fatherhood: "Pregnancy and childbirth were very male experiences for me. When I birthed my children, I was born into fatherhood" (29-year-old, no prior testosterone use). Participants often used words such as "dad," "carrier," and "gestational parent" to affirm their male gender identity and describe their parenting role.

Feelings of isolation were common. One participant stated, "Pregnancy came with feelings of isolation and limitation" (28-year-old, prior testosterone use). Some identified the source of isolation as stemming from feeling "lonely because I was the only one" (30-year-old, prior testosterone use). These feelings were contextualized by comments about "lack of support" and "lack of resources available to pregnant transgender men." This isolation was also referenced in terms of invisibility: "I passed as 'not pregnant' until my eighth month, because I'm chubby anyways, and because people don't assume that someone who looks like me could be pregnant" (34-year-old, no prior testosterone use). As another participant simply put it: "We exist. And we are different" (35-year-old, prior testosterone use).

Another theme that emerged was the relationship between gender dysphoria and pregnancy. Some participants reported improvements in gender dysphoria, feeling new connections with their bodies: "It was relieving to feel comfortable in the body I'd been born with" (20-year-old, no prior testosterone use). Others felt an increase in dysphoria, and for some, that dysphoria continued into the postpartum period: "Heavy time, having a baby, not passing as male, all the changes and a society telling me to just be happy"

Table 3. Fertility Experiences Surrounding Most Recent Pregnancy by Prior Testosterone Use

Characteristic	Total (N=41)	Prior Testosterone Use		P
		Yes (n=25)	No (n=16)	
Planned pregnancy	28 (68)	19 (76)	9 (56)	.3
Contraception use before this pregnancy*†				.03
Condoms	16 (41)	10 (40)	6 (43)	
None	15 (38)	12 (48)	3 (21)	
Abstinence‡	3 (7)	3 (12)	0	
Fertility awareness	2 (8)	0	2 (14)	
Combined hormonal contraception (OCPs, transdermal patch, vaginal ring)	1 (3)	0	1 (7)	
Injection, intrauterine device, implant	1 (3)	0	1 (6)	
Partner had vasectomy	1 (3)	0	1 (6)	
Time to conception (mo)†				.14
Unplanned pregnancy	13 (32)	6 (24)	7 (44)	
Less than 1	3 (17)	1 (20)	2 (12)	
1–3	9 (22)	8 (32)	1 (6)	
4–6	8 (19)	5 (20)	3 (19)	
More than 7	4 (10)	1 (4)	3 (18)	
Source of oocyte				.12
Own ovaries	36 (88)	21 (84)	15 (94)	
Significant other or spouse	4 (10)	4 (16)	0	
Anonymous donor	1 (2)	0	1 (6)	
Source of sperm				.5
Significant other, spouse, or romantic partner	31 (76)	17 (68)	14 (88)	
Known donor	4 (10)	3 (12)	1 (6)	
Anonymous donor or sperm bank	6 (15)	5 (20)	1 (6)	
Medical intervention to become pregnant§				
Consultation	6 (15)	4 (16)	2 (12)	
Fertility drugs	3 (7)	2 (8)	1 (6)	
Assisted reproductive technology‖	5 (12)	5 (20)	0	

OCP, oral contraceptive pill.
Data are n (%) unless otherwise specified.
* Participants were given the option to identify with more than one, so total exceeds 100%.
† Not all the participants answered this question.
‡ Defined as not having penile–vaginal intercourse.
§ Participants could mark more than one, therefore not comparing the results statistically.
‖ Includes artificial insemination, in vitro fertilization, and gamete intrafallopian transfer.

(35-year-old, prior testosterone use). Combined with feelings of isolation postpartum, many participants specifically mentioned having postpartum depression. "Began to show symptoms of postpartum depression long before anyone discussed symptoms to watch for… Began researching and working through postpartum depression issues independently; found no professional with familiarity with 'trans/genderqueer' gestational parents" (28-year-old, prior testosterone use). As mentioned, the depression seemed amplified by a lack of gender-sensitive resources for postpartum depression.

In response to queries interactions with health care providers, some participants mentioned positive interactions with their health care teams regarding their gender identity. "I was always called 'he,' I was always called 'dad,' and my body parts were called by the words I used" (34-year-old, prior testosterone use). As previously, positive experiences often focused on proper use of gender-related language. Other participants mentioned negative experiences that ranged from improper pronoun use and rude treatment to being turned away from medical practices and denied treatment. In one extreme experience, a participant reported that "Child Protection Services was alerted to the fact a 'tranny' had a baby" (21-year-old, prior testosterone use). Many participants called for better treatment from the health care system through acknowledging the unique identities of pregnant transgender men and grounding health care provider–patient interactions in compassion and respect. As one participant said, "treat us as if we are normal human beings with normal bodies" (37-year-old, no prior testosterone use). Additionally, participants

Table 4. Pregnancy Experience and Neonatal Outcomes

Characteristic	Total (N=41)	Prior Testosterone Use		P
		Yes (n=25)	No (n=16)	
Source of prenatal care*				1.0
Obstetrician	16 (40)	9 (38)	7 (44)	
Certified nurse midwife	11 (28)	7 (29)	4 (25)	
Lay midwife	7 (18)	4 (17)	3 (19)	
Family practice doctor	4 (10)	3 (13)	1 (6)	
No prenatal care	2 (5)	1 (4)	1 (6)	
Perinatal complications†				
Hypertension	5 (12)	4 (16)	1 (6)	
Preterm labor	4 (10)	3 (12)	1 (6)	
Placental abruption	4 (10)	2 (8)	2 (12)	
Anemia	3 (7)	0	3 (19)	
Gestational diabetes	2 (5)	2 (8)	0	
Multiple pregnancy‡	2 (5)	2 (8)	0	
Postpartum infection	2 (5)	1 (4)	1 (6)	
Premature rupture of membranes	1 (2)	0	1 (6)	
Pyelonephritis	1 (2)	1 (4)	0	
Uterine rupture	1 (2)	1 (4)	0	
Substance use§				
Cigarettes	3 (7)	2 (8)	1 (6)	1.0
Alcohol	1 (2)	1 (4)	0	1.0
Recreational drugs	1 (2)	0	1 (6)	.6
Gestational age at delivery (wk±d)	38±6	37±9	39±5	.4
Location of birth				.6
Hospital	32 (78)	18 (72)	14 (88)	
Home	7 (17)	5 (20)	2 (13)	
Independent birth center	2 (5)	2 (8)	0	
Underwent labor induction	9 (22)	7 (28)	2 (12)	.3
Method of delivery				.5
Vaginal	29 (71)	16 (64)	13 (81)	
Cesarean	12 (30)	9 (36)	3 (19)	
Reason for cesarean delivery				.6
Previous cesarean delivery	1 (8)	1 (11)	0	
Breech presentation	1 (8)	1 (11)	0	
Placenta previa	1 (8)	1 (11)	0	
Arrest of labor	2 (17)	1 (11)	1 (33)	
Multiple pregnancy (twins)	1 (8)	1 (11)	0	
Requested cesarean delivery	3 (25)	3 (33)	0	
Other‖	3 (25)	1 (11)	2 (66)	
Birth weight (g)¶	3,146±1,671	2,914±1,276	3,490±625	.2
Neonate admitted to the NICU*	5 (14)	4 (20)	1 (7)	.4
Neonate diagnosed with an anomaly or developmental disorder*#	3 (9)	1 (5)	2 (14)	.7
Neonate diagnosed with a disorder of sexual development**	2 (6)	1 (5)	1 (7)	.8
Chest (breast) fed	21 (51)	10 (40)	11 (69)	.04

NICU, neonatal intensive care unit.
Data are n (%) or mean±standard deviation unless otherwise specified.
* Not all the participants answered this question.
† Includes complications occurring in the preconception, antepartum, intrapartum, and postpartum periods.
‡ Both sets of multiples were twins.
§ Survey question stated: "Once you knew you were pregnant, did you regularly: _ drink alcohol, _ smoke cigarettes, _ use recreational drugs, _ none of the above."
‖ Other reasons for cesarean delivery: placental abruption (n=1), preeclampsia (n=1), none specified (n=1).
¶ N=42 neonates resulting from a set of twins.
# Ventricular septal defect (n=1), bone cancer (n=1), sensory integration disorder (n=1).
** Intersex (n=1), micropenis (n=1).

noted that although their specific health care provider(s) may have been transgender-friendly, this was not necessarily the case with the office staff, nurses, and other health care workers.

DISCUSSION

The College has highlighted the need for obstetrician–gynecologists to help eliminate barriers to care for transgender men.[2] Our results demonstrate that transgender men desire children[4] and are willing and able to conceive, carry a pregnancy, and give birth. Participants repeatedly expressed a desire for more information regarding fertility options and access to reproductive health care providers who respect, support, and understand their gender identity.

Studies suggest that amenorrhea commonly occurs within 6 months of initiating testosterone therapy.[12,13] However, timeframe for resumption of menses after cessation of testosterone is unclear, and some have stated amenorrhea may be irreversible.[14] Participants who discontinued testosterone to attempt pregnancy reported resumption of menses within 6 months, with the majority within 3 months. Some conceived before return of menses. Despite small sample size, the timeline for menses resumption is consistent with that of literature on women who became amenorrheic with Sertoli-Leydig tumors and resumed menses after tumor resection.[15]

Although most transgender men in this study received prenatal care from a physician and delivered in a hospital, participants used nonphysician providers and nonhospital birth locations more frequently than the general public. In 2009, 99% of U.S. births occurred in hospitals,[16] compared with 78% of our participants. It is possible that health care provider choice and delivery location were responses to actual or anticipated negative experiences as suggested from many qualitative reports of suboptimal interactions with health care providers. However, health care provider and birth location may have resulted from other barriers such as access to health insurance.[17–20] Further research to clarify the experiences of transgender men with peripartum service provision will provide guidance for meeting their needs.

There is a 12% prevalence of major depressive disorders surrounding pregnancy, including postpartum depression, for women in the United States.[21] Although we did not specifically ask about depressive disorders, many of our participants reported experiences with peripartum depression in the narrative responses. A Canadian study of mental health among transgender men (n=207) found that depression was common.[22] Our findings suggest that transgender men may represent a high-risk population for postpartum depression and, although further research is warranted, future recommendations should emphasize assessment of peripartum depression in this population.

Nearly half of the transgender men who had not used testosterone had an unplanned pregnancy, a proportion comparable to that of the U.S. population.[23] Comparatively, one fourth of those previously on testosterone had unplanned pregnancies. By design this study cannot speak to incidence or prevalence of unplanned pregnancies among transgender men. However, given the financial burden[24] and risk of increased morbidity[25] from unintended pregnancy as well as the contraindication of testosterone use during pregnancy,[26,27] these findings suggest a potential unmet need for contraceptive services for transgender men.

Limitations to this study include those inherent with an online, cross-sectional survey, including not allowing for follow-up clarification from participants, decreasing responses from those with low literacy or other barriers to taking an online survey, and self-reported data raising concern for recall bias. The limited socioeconomic and racial diversity in respondents reduces immediate generalizability. Lastly, our eligibility criteria screened for transgender men who had a successful birth, impeding generalizable to those who attempt to get pregnant and cannot and those who do not carry to term. Strengths include the novelty of reporting transgender men's pregnancy experiences, inclusion of those who had socially and medically transitioned, and the mixed-methods format that allows insight into experiences.

Through demonstrating that transgender men are becoming pregnant and having babies, regardless of prior testosterone use, this preliminary study contributes data to emerging discussions regarding their reproductive health experiences. Respondents highlight the need for health care providers to partner with this community and develop gender-appropriate resources and support. Simple but meaningful steps for health care providers include establishing rapport by using patients' preferred names and pronouns, validating gender identity, and reflecting their individual relationships to their pregnancies. Counseling with transgender men should include discussions of reproductive goals, including fertility desires, and the role of contraception. We also suggest all health care providers discuss fertility preservation options with patients before initiating testosterone use in accordance with international standards of care.[26,27] More

clinical and investigational work is needed to understand the physical and emotional needs of transgender men during pregnancy and birth so that health care providers may partner with this underserved community to improve care. As we respond to calls for increased access to reproductive health care for transgender men, we must ensure that we can provide evidence-based, comprehensive services befitting their unique needs and concerns.[2]

REFERENCES

1. Grant JM, Mottet LA, Tanis J, Herman JL, Harrison J, Keisling M. National transgender discrimination survey report on health and healthcare. Washington (DC): National Center for Transgender Equality and National Gay and Lesbian Task Force; 2010. p. 1–23.
2. Healthcare for transgender individuals. Committee Opinion No. 512. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;118:1454–8.
3. Scheim A, Greta B. Sex and Gender Diversity Among Transgender Persons in Ontario, Canada: Results From a Respondent-Driven Sampling Survey. J Sex Res 2014;1–14 [Epub ahead of print].
4. Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedecker D, Van de Peer F, et al. Reproductive wish in transsexual men. Hum Reprod 2012;27:483–7.
5. Califia-Rice P. Family values: two dads with a difference –neither of us was born male. Village Voice June 20, 2000.
6. Hembree WC, Cohen-Kettenis P, Delemarre HA, Gooren LJ, Meyer WJ III, Spack NP, et al. Endocrine treatment of transsexual persons. Minneapolis (MN): WPATH (World Professional Association for Transgender Health); 2009.
7. Beatie T. Labor of love: the story of one mans extraordinary pregnancy. Berkeley (CA): Seal Press; 2008.
8. De Sutter P. Gender reassignment and assisted reproduction present and future reproductive options for transsexual people. Hum Reprod 2001;16:612–4.
9. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
10. Charmaz K. Constructing grounded theory: a practical guide through qualitative analysis. Thousand Oaks (CA): Pine Forge Press; 2006.
11. Pequegnat W, Rosser B, Bowen A, Bull S, DiClemente R, Bockting W, et al. Conducting internet-based HIV/STD prevention survey research: considerations in design and evaluation. AIDS Behav 2007;11:505–21.
12. Nakamura A, Watanabe M, Sugimoto M, Sako T, Mahmood S, Kaku H, et al. Dose-response analysis of testosterone replacement therapy in patients with female to male gender identity disorder. Endocr J 2013;60:275–81.
13. Steinle K. Hormonal management of the female-to-male transgender patient. J Midwifery Womens Health 2011;56:293–302.
14. T'Sjoen G, Van Caenegem E, Wierckx K. Transgenderism and reproduction. Curr Opin Endocrinol Diabetes Obes 2013;20:575–9.
15. Gui T, Cao D, Shen K, Yang J, Zhang Y, Yu Q, et al. A clinicopathological analysis of 40 cases of ovarian Sertoli–Leydig cell tumors. Gynecol Oncol 2012;127:384–9.
16. Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Kirmeyer S, Mathews TJ, et al. Births: final data for 2009. Natl Vital Stat Rep 2011;60:1–70.
17. Unger C. Care of the transgender patient: the role of the gynecologist. Am J Obstet Gynecol 2014;210:16–26.
18. Dutton L, Koenig K, Fennie K. Gynecologic care of the female-to-male transgender man. J Midwifery Womens Health 2008;53:331–7.
19. Poteat T, German D, Kerrigan D. Managing uncertainty: a grounded theory of stigma in transgender healthcare encounters. Soc Sci Med 2013;84:22–9.
20. Xavier J, Bradford J, Hendricks M, Safford L, McKee R, Martin E, et al. Transgender healthcare access in Virginia: a qualitative study. Int J Transgenderism 2013;14:3–17.
21. Le Strat Y, Dubertret C, Le Foll B. Prevalence and correlates of major depressive episode in pregnant and postpartum women in the United States. J Affect Disord 2011;135:128–38.
22. Rotondi NK, Bauer GR, Travers R, Travers A, Scanlon K, Kaay M. Depression in male-to-female transgender Ontarians: results from the trans PULSE project. Can J Commun Ment Health 2011;30:113–33.
23. Finer LB, Kost K. Unintended pregnancy rates at the state level. Perspect Sex Reprod Health 2011;43:78–87.
24. Trussell J, Henry N, Hassan F, Prezioso A, Law A, Filonenko A. Burden of unintended pregnancy in the United States: potential savings with increased use of long-acting reversible contraception. Contraception 2013;87:154–61.
25. Shah PS, Balkhair T, Ohlsson A, Beyene J, Scott F, Frick C. Intention to become pregnant and low birth weight and preterm birth: a systematic review. Matern Child Health J 2011;15:205–16.
26. Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. Int J Transgenderism 2012;13:165–232.
27. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ III, Spack NP, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2009;94:3132–54.
28. Kuper L, Nussbaum R, Mustanski B. Exploring the diversity of gender and sexual orientation identities in an online sample of transgender individuals. J Sex Res 2012;49:244–54.
29. Djordjevic M, Stanojevic D, Bizic M, Kojovic V, Majstorovic M, Vujovic S, et al. Metoidioplasty as a single stage sex reassignment surgery in female transsexuals: Belgrade experience. J Sex Med 2009;6:1306–13.

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REVIEW ARTICLE

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Androlgy of male-to-female transsexuals: influence of cross-sex hormone therapy on testicular function

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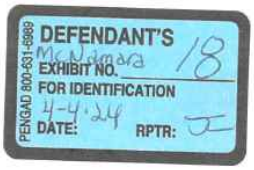


SUMMARY

Patients with gender dysphoria are offered cross-sex hormone therapy and sex reassignment surgery to achieve the transition between the sex assigned at birth and gender identity. According to international guidelines, cross-sex hormone therapy in trans-women should lead to a psychologically and physiologically healthy body with feminized serum hormone levels, resulting in suppression of spermatogenesis. However, in a recently published multi-center study, we discovered a high proportion of patients with male serum hormone levels and qualitatively intact spermatogenesis on the day of sex reassignment surgery. The objective of this study was to review the content of 11 publications that focus on the influence of cross-sex hormone therapy on testicular morphology. These publications were identified based on a PubMed search for the key words transgender/transsexual/gender dysphoria in male-to-female persons, cross-sex hormone therapy, and testicular tissues. Whereas three publications described a marked reduction of the spermatogenic level in all patients examined, eight publications reported inconsistent results. Histological analyses showed highly variable outcomes from qualitatively normal spermatogenesis and undisturbed Leydig/Sertoli cell morphology to full testicular regression with severe cellular damage and hyalinization. Explanations for these heterogeneous findings include insufficient cross-sex hormone therapy regarding dosage or duration. As complete spermatogenesis is associated with virilized serum hormone levels, these patients may face challenges especially after sex reassignment surgery in adjusting to the abruptly established hypogonadal state following removal of the testes. These findings also suggest that contraception should be discussed, and fertility preservation should be offered during/prior to cross-sex hormone therapy. There is a need for more individualized and better-controlled cross-sex hormone therapy and post-treatment regimens. Evidence-based guidelines for attending clinicians need to be established in order to deliver the most appropriate care.

INTRODUCTION

Gender identity is the personal identification and sense of being male or female, independent of the sex assigned at birth (Fabris *et al.*, 2015). Patients suffering from gender dysphoria (GD) experience the distressing scenario of incongruence between the gender assigned at birth and the personal identification. The etiology of GD remains hitherto unknown (Gooren, 2011). Nonetheless, the urge to live in the opposite gender can be a distressing scenario and treatment requires hormonal, anatomical, legal, and psychosocial adaptations (Gooren *et al.*, 2008; Kuyper & Wijsen, 2014). Hence, patients with GD seek treatment and guidance from different experts and allied health professionals within the medical field.

In recent years, treatment of GD patients has become a topic of increasing medical relevance as more and more patients were referred for treatment (Judge *et al.*, 2014). Other studies confirmed that the prevalence has indeed increased over the past 50 years (Arcelus *et al.*, 2015). In a systematic review and meta-analysis, it was concluded that globally 4.6 in 100.000 individuals (6.8 for trans-women and 2.6 for trans-men) were transsexual and requested medical advice or treatment (Arcelus *et al.*, 2015).

The mean age at presentation appears to be similar throughout Europe with 36.3 years in Sweden (Dhejne *et al.*, 2011) and 32.6 years in Ireland (Judge *et al.*, 2014). However, 61.9% of patients declared their age of self-diagnosis as being pre-pubertal (Byne *et al.*, 2012). While literature does not suggest that the age distribution at presentation is bimodal with a pre-pubertal

and an older adult age group, a recent study suggests that the number of young patients at the time of presentation is indeed increasing (Judge *et al.*, 2014).

The complex care pathways of trans-individuals render the organization of medical service difficult (Arcelus *et al.*, 2015). When clinicians attempt to assess treatment protocols for the care of GD patients, two challenges become apparent: the absence of criteria whom to treat and the lack of consensus how to treat (Gorin-Lazard *et al.*, 2012). In Germany, the new guidelines of the Association of the Scientific Medical Societies (AWMF-guideline) are still in process. Up to now, the caring doctor has to rely on the international and European guidelines of the Endocrine Society and the World Professional Association of Transgender Health (WPATH). According to the European guidelines of the Endocrine Society, the treatment consists of diagnostic assessment, psychotherapy or counseling, real-life experience, cross-sex hormone therapy (CHT), and surgical therapy, which presents the final step in the process of phenotypical transition (Hembree *et al.*, 2009). A listing with recommendation from various bodies is presented in Table S1. A more specific and applicable recommendation is provided by the WPATH (Version 7): This authority introduces four defined criteria to be fulfilled prior to CHT: 1. The subject should have a persistent, well-documented GD according to the Diagnostic and Statistical Manual of Mental Disorders V. 2. He/she should have the capacity to make a fully informed decision and to consent to treatment. 3. He/she should have the age of majority (in Germany 18 years of age). 4. Medical or mental health concerns must be reasonably controlled (WPATH, 2011). Regarding criterium 3, it is important to note that some countries also allow treatment of children and young adolescents (using GnRH analogues), provided that they fulfill respective criteria and under the auspices of an ethics committee and/or legislation. This early treatment leads to a gradual regression of sex characteristic development, thereby prolonging the diagnostic phase as the body remains in a neutral early pubertal state (Fisher *et al.*, 2016). Since surgical intervention is only possible at the age of 18, data on the effects of these interventions on testicular tissues are not available.

To date, the procedure of CHT in GD patients is not fully standardized. Reasons for this include lack of controlled clinical trials on feminizing/masculinizing hormone regimens and the safety or efficacy in achieving physical transition (WPATH 2011, Meriggiola & Berra, 2013). The optimal steroid hormone treatment regime for transsexual subjects has also not yet been described (van Kesteren *et al.*, 1997). Recommendations for management are therefore based on expert opinion (Gooren *et al.*, 2008). To offer a personalized treatment, type of formulation, hormone dosage, and route of administration (oral, transdermal, or intramuscular) are variable (Wierckx *et al.*, 2014b). The existing variations in treatment modalities and the small number of subjects treated in each clinic render it difficult to collect valid data on the beneficial effects as well as unwanted side effects of CHT (Wierckx *et al.*, 2014b) and sex-reassignment surgery (SRS).

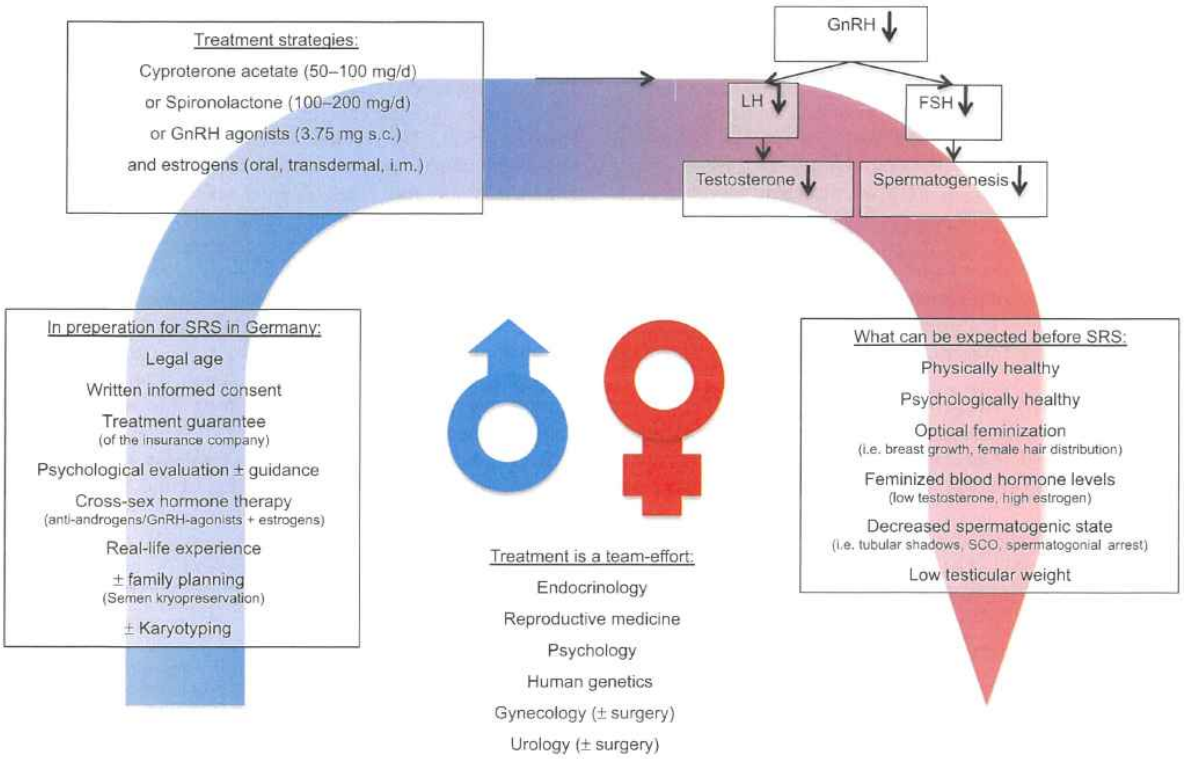
CROSS-SEX HORMONE THERAPY (CHT)

For MtF patients, 'devirilization' using Cyproteron acetate (CPA) followed by 'feminization' using estrogens combined with anti-androgens is most commonly used (Gorin-Lazard *et al.*, 2012) (Fig. 1). CPA is a synthetic testosterone antagonist and acts as an anti-androgen and progestin. Persistently high serum levels of CPA lead to a down regulation of the hypothalamic gonadotropin releasing hormone (GnRH) activity and block gonadotropin release from the pituitary finally inhibiting testosterone release from testicular Leydig cells. Studies focusing the influence of hormonal treatments in prostate cancer patients revealed that GnRH agonists in biological men lead to a decrease of serum testosterone to castration levels within 2–3 weeks (Labrie *et al.*, 2005). Based on male contraceptive studies, however, GnRH analogues can suppress spermatogenesis only mildly, if used alone (Nieschlag *et al.*, 2004). In contrast, it has been demonstrated that CPA can be considered a potent progestin and suppresses spermatogenesis effectively also in humans (Fogh *et al.*, 1979; Moltz *et al.*, 1980; Wang & Yeung, 1980; Meriggiola *et al.*, 1998). Peripheral total and free testosterone and 5-α-dihydrotestosterone may reach very low levels leading to the desired effects on sexuality and androgen-dependent body functions (Turner *et al.*, 2013) (Fig. 1). Estrogen can be given orally as conjugated estrogens, or 17-β-estradiol, as transdermal estrogen, or parenteral estrogen esters (Hembree *et al.*, 2009).

Regarding treatment doses, the Endocrine Society recommends the prescription of either anti-androgens (Spironolactone 100–200 mg/day or Cyproterone acetate 50–100 mg/day) or GnRH agonists (3.75 mg s.c. monthly) for down regulation of the hyopthalamic–pituitary–adrenal axis. CPA is primarily used in Europe, whereas Spironolactone is favored in the USA. To achieve efficient suppression, both anti-androgenic drugs need to be taken on a regular basis at least several times per week if not daily. GnRH analogue therapy is expensive, but provides access to long-lasting formulations providing a more controlled long-lasting suppression (Meriggiola & Berra, 2013). Female sex steroid replacement is reached by estrogen preparations (oral estradiol: 2.0–6.0 mg/day; transdermal estradiol: 0.1–0.4 mg twice weekly; parenteral estradiol: 5–20 mg i.m. every 2nd week) (Hembree *et al.*, 2009) (Fig. 1).

It is of utmost importance to screen all patients before starting CHT to exclude underlying diseases (i.e. clotting disorders, osteoporosis, obesity, osteoporosis, hypertension, breast cancer), which rule out estrogen treatment of any kind. Venous thromboembolism is the most serious complication and incidents have been reported for both transdermal and oral estradiol (Meriggiola & Gava, 2015). If taken accordingly, the anti-androgens reduce endogenous testosterone levels. Serum testosterone levels should be lowered to the female range (<55 ng/dL), and serum estradiol should be increased to the mean serum level for pre-menopausal women (<200 pg/mL) (De Sutter, 2001; Hembree *et al.*, 2009; Meriggiola & Berra, 2013). With testosterone and free testosterone efficiently suppressed, sex hormone-binding globuline (SHBG) levels decrease. If anti-androgen medication is taken accordingly furthermore, SHBG levels will remain low thereafter. If patients take oral estrogen treatment SHBG will increase, in contrast to transdermal estrogen treatment (Wierckx *et al.* 2014b). Extensive studies applying CHT confirmed that testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) are significantly suppressed (Giltay & Gooren, 2000; Fuss *et al.*, 2015). It was recommended to use LH as an indicator to monitor the adequacy of sex steroid administration (Gooren *et al.*, 2008). Under estrogen replacement, the synthesis and the release of prolactin from the pituitary is stimulated in a dose- and time-dependent fashion (Bunck *et al.*, 2009). How

Figure 1 Requirements, treatment strategies, and targets of cross-sex hormone treatment of patients with gender dysphoria. Abbreviations stand for: GnRH: Gonadotropin releasing hormone, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, SCO: Sertoli cell only.



long CHT should be provided before SRS is a matter of debate. We performed a multi-center study revealing that some clinics advise their patients to terminate CHT several weeks prior to SRS, whereas other clinics advise continued treatment until the day of surgery (Schneider *et al.*, 2015). Reasons for discontinuation of CHT include the fear of increased bleeding during surgery or complications of wound healing in post-operative care (Hess *et al.*, 2014). Increased bleeding as a result of sex hormone exposure has no rational basis. In our study, we found a highly diverse outcome: More feminized hormonal levels (low testosterone, high estradiol levels) on the day of SRS were seen with continued CHT. In contrast, termination of CHT days or weeks prior to SRS leads to a partial or full masculine hormone profile (Schneider *et al.*, 2015). Several questions remain unanswered: Do different male or female hormone patterns on the day of SRS have any implications for the well-being of the individual patient prior or post-surgery? Is the potential surgical risk (i.e. bleeding risk, pharmacological interference) for terminating SRS balanced against the sudden withdrawal of sex steroids following SRS?

PHYSIOLOGICAL EFFECTS INDUCED BY CHT AND SEX REASSIGNMENT

Physical changes that may occur in the first 3–6 months of CHT include redistribution of body fat mass decreased libido, oiliness of skin, breast tissue growth, and reduction of facial and body hair. Maximum breast development is generally achieved 2 years after initiation of hormone treatment (Hembree *et al.*, 2009). A decrease in LH and FSH in combination with the exogenous steroid levels during CHT leads to weight gain, gynecomastia, and lethargy, as well as a decrease in sexual interests and sexual fantasies (Meriggiola *et al.*, 1998). Total bodyweight remained unchanged for MtF transsexuals, although they experienced an increase in total body fat mass and a decrease in total body lean mass ($n = 32$) (Wierckx *et al.*, 2014b). Increased serum leptin levels may influence eating habits in MtF subjects under CHT (Elbers *et al.*, 1997). The majority of male-to-female transsexuals reported a decrease in sexual desire after treatment (Wierckx *et al.*, 2011, 2014a). A decline in serum testosterone levels or testosterone action together with increased SHBG and high estradiol levels may be responsible for this low sexual desire (Wierckx *et al.*, 2014b).

EFFECT OF CHT ON TESTICULAR MORPHOLOGY

Anticipated effects of CHT on the testis can be derived from male contraception studies demonstrating that gonadotropin suppression leads to spermatogenic suppression (Bremner, 2012). Importantly, this effect on spermatogenesis was fully reversible in biological men with sperm recovery to the thresholds of 20 million/mL within 3.4 months (Liu *et al.*, 2006). With regard to transgender patients, these data suggest that discontinuation of anti-androgen treatment prior to SRS will result in an increase of intra-testicular and serum testosterone levels and a re-initiation of spermatogenesis.

In addition, elevated peripheral estrogen levels have diverse effects on male reproductive organs. Changes were observed regarding the rete testis, efferent ducts, and to a lesser degree, the epididymis and Leydig cells (Sapino *et al.*, 1987). With regard to the germ cells, exogenous doses of 20 μg/day of ethinylestradiol had no negative effect on sperm motility and sperm density, whereas higher doses (60 μg/day) lead to a reduction of sperm motility after a few days. After 2 weeks, also sperm counts were affected by high doses of estrogens (Lubbert *et al.*, 1992).

The actual influence of CHT on testicular morphology in male-to-female (MtF) GD patients has been described in 11 publications to date with very different outcomes (Table 1). While some patients showed severe involution of spermatogenesis as well as Leydig cells, other patients maintained qualitatively complete spermatogenesis with normal Leydig cell abundance (Payer *et al.*, 1979; Thiagaraj *et al.*, 1987; Venizelos & Paradinas, 1988).

More specifically, Thiagaraj *et al.* (1987) reported that three of 10 patients did not respond to CHT, based on unchanged testicular volumes and testicular histology (Thiagaraj *et al.*, 1987). This contrasts to a study in which the testes of four patients were analyzed and showed primarily Sertoli-cell only tubules with occasional spermatogonia in individual seminiferous tubules (Lu & Steinberger, 1978). In line with this, Schulze (1988) reported about 12 subjects who showed a uniform and strong testicular involution. Complete spermatogenic depletion was shown as no differentiating germ cells were detected, and the seminiferous tubules contained exclusively Sertoli cells and spermatogonia. The tubules, were decreased in diameter, showed no lumen, and were surrounded by an extensively thickened lamina propria. Finally, Leydig cells were not detected in these testicular tissues (Schulze, 1988). This latter finding led the author to suggest that the treatment causes mature Leydig cells to de-differentiate into Leydig cell precursor cells with a fibroblast-like appearance (Schulze, 1988). Functionally, androgen production of Leydig cells may be altered by estrogens via two different mechanisms. Estrogens may have a direct effect on Leydig cells or may act indirectly via suppression of gonadotropins. The latter effect is likely long term and requires higher doses (Rodriguez-Rigau *et al.*, 1977).

In our own study, we analyzed testicular tissues of 108 patients. We confirmed the variability of the spermatogenic

Table 1 Publications examining the influence of cross-sex hormone therapy on testicular morphology in gender dysphoria patients

	Year	First author	Country	Patient number	Treatment	Results
1	1977	Rodriguez-Rigau *et al.*	Houston, USA	$n = 1$	Ethinylestradiol estradiol of 0.5–1 mg daily for 18 months	Germinal cells were absent, except very occasional spermatogonia, seminiferous tubules were reduced in diameter, heavy hyalinization and fibrosis. Atrophy of interstitial area with the absence of recognizable Leydig cells.
2	1978	Lu *et al.*	Houston, USA	$n = 4$	Long term treatment with ethinylestradiol (1–2 mg) daily	The estrogen-treated testicular tissue contained only Sertoli cells and very few spermatogonia within the seminiferous tubules.
3	1979	Payer *et al.*	Galveston, USA	$n = 6$	Steroid hormones ranging from 1.25 to 7 years	Inconsistent results: Reduced spermatogenesis and reduced numbers of Leydig cells to complete spermatogenesis with normal Leydig cell abundancy.
4	1987	Thiagaraj *et al.*	Singapore	$n = 10$	Estrogen therapy (0.05–0.2 mg daily) for 6–13 years. Treatment was stopped 2 weeks before SRS	3 cases of normal spermatogenic activity with normal Leydig cells and 7 cases of total absence of spermatogenic activity with reduced Leydig cells.
5	1988	Venizelos *et al.*	London, UK	$n = 5$	Estrogen treatment for periods ranging from 18 months till 5.5 years	Leydig cell population was reduced in all patients. Tubular hyalinization was present in all patients. Spermatogenic levels varied.
6	1987	Sapino *et al.*	Turin, Italy	$n = 5$	40–50 mg/week of polyestradiol phosphate treatment for varying periods. Withdrawal 10 days before SRS.	Atrophy of the seminiferous tubules was observed in all cases; its degree, and a marked decrease in Leydig cells, correlated with low plasma gonadotropin levels.
7	1988	Schulze *et al.*	Hamburg, Germany	$n = 11$	1–12 years of treatment with various amounts of estrogens, estradiol, or ethinylestradiol	Narrow seminiferous cords surrounded by an extensively thickened lamina propria. They contain Sertoli cells and spermatogonia exclusively. There is no evidence of typical Leydig cells.
8	1990	Kisman *et al.*	Amsterdam, The Netherlands	$n = 8$	18 months with a combination of 100 g ethinylestradiol and 100 mg CPA daily	Increase of interstitial tissue, decrease in number and in volume of Leydig cells and spermatogenic arrest
9	1992	Lübbert *et al.*	Berlin, Germany	$n = 1$	20 ug and 60 ug of ethinylestradiol	The low dose had no negative effect on sperm motility? and density. High dose reduced motility after a few days and density after 2 weeks.
10	2004	Aschim *et al.*	Oslo, Norway	$n = 3$	100 ug ethinylestradiol for at least 1 year	Dramatic decrease of estrogen receptor beta transcripts.
11	2015	Schneider *et al.*	Münster, Germany	$n = 108$	Anti-androgens (10–100 mg) combined with different dosages of estrogens or only estrogens or a combination of Spironolactone and estrogens. Multicenter study: Patients either discontinued treatment 6 weeks (clinic A) or 2 weeks (clinic B) prior to SRS or not at all (clinic C).	Histology revealed a highly heterogeneous picture with 24% patients with normal spermatogenesis irrespective of the treatment strategy. Only patients that did not discontinue hormonal treatment showed feminized blood levels on the day of SRS and the lowest ITT levels.

involution under CHT based on differing testicular weights and corresponding degrees of germ cell depletion (Schneider *et al.*, 2015). In 24% of the patients, we found qualitatively complete spermatogenesis on the day of SRS. The majority of patients, however, showed an obvious involution down to a Sertoli-cell-only phenotype and fully hyalinized seminiferous tubules (tubular shadows). The status of spermatogenesis, in terms of the most advanced germ cell type, did not correlate to the levels of intratesticular testosterone. As testicular tissues were obtained from three different clinics with distinct treatment regimens prior to SRS, we compared the three patient groups that either discontinued CHT a couple of weeks prior to SRS or underwent continuous CHT. Only those patients with a continuous CHT showed feminized blood levels and low intratesticular testosterone levels on the day of SRS. Intriguingly though, these data were independent of the degree of the histologically detectable spermatogenic involution indicating that the endocrine process can be reverted to a male pattern in just a few weeks, whereas the spermatogenic involution will persist for a longer period (Schneider *et al.*, 2015) (Table 1).

Importantly, as the testicular volume should decrease by 25% within the first year of therapy due to depletion of germ cells, this decline in testis weight represents a valid readout of the efficiency of spermatogenic suppression (Mayerhofer, 2013; Schneider *et al.*, 2015).

In children treated with GnRH agonists, a decrease of testicular volume in 43 of 49 patients was found (Schagen *et al.*, 2016). The proliferation of the pre-pubertal testis is caused by gonadotropin secretion. Plant *et al.* demonstrated in pre-pubertal Rhesus monkeys that spermatogonial proliferation, the increase of Sertoli cells, the number and morphology of Leydig cells is gonadotropin dependent and consequently so is the testosterone secretion. Hence, suppressing gonadotropins early in the development might hinder the preparation of the adult testis (Plant *et al.*, 2005).

SEX-REASSIGNMENT SURGERY AND POSTOPERATIVE CARE

Presently, the surgeon performing SRS is not obliged to control that a feminized serum hormone profile has been achieved by CHT and that spermatogenesis is regressed. This could be easily assessed by palpation to confirm the presence of small testes. Unger (2014) suggests that surgeons should choose their patients carefully and with appropriate scrutiny (Unger, 2014). In Germany, patients responded with subjective satisfaction to SRS and appreciated the good operative results indicating that SRS has a positive effect on the post-surgical life (Hess *et al.*, 2014). Following SRS, including orchiectomy, hormonal therapy must be continued according to guidelines (Hembree *et al.*, 2009). However, sex hormone levels are rarely monitored post-surgically albeit it is important to maintain sex steroid-dependent physiological functions (Meriggiola & Berra, 2013). This however, is of particular importance as surgeons in some clinics in Germany (gynecologist, urologist, reconstructive surgeon), who have not been part of the treatment prior to surgery, advice patients to stop CHT prior to SRS in fear of complications during surgery as mentioned above.

In particular in these cases, adequate care should include a personalized sex hormone replacement therapy for the abruptly gonadectomized individual. This may include temporal substitution with male sex steroids to provide a slow and steady transition as well as testing of various sex-steroid replacement regimens leading to best satisfaction of the individual. Further research is needed to correlate endocrine and physiological features in GD individuals to optimize pre- and post-surgical care.

PSYCHOLOGICAL EFFECTS OF SEX REASSIGNMENT

No significant psychopathologies have been reported in pre- and post-operative assessments of GD patients under CHT (Heylens *et al.*, 2014). However, primarily after initiation of CHT, the majority of patients reported to be in better mood, they were happier, and less anxious (Heylens *et al.*, 2014). Also, they appeared more self-confident and encountered a better body-related experience, indicating a less distorted self-image (Fisher *et al.*, 2014; Heylens *et al.*, 2014). The most important effect resulted from the confirmation of the diagnosis and the initiation of hormone therapy (Heylens *et al.*, 2014).

However, a Swedish study showed that GD patients after SRS have considerably higher risks of mortality, suicidal behavior, and psychiatric morbidity compared to the general population (Dhejne *et al.*, 2011). This study suggests that sex reassignment, although alleviating GD, may not suffice as treatment for transsexualism. Instead, improved psychiatric and somatic care after sex reassignment for this patient group appear to be necessary (Dhejne *et al.*, 2011). In contrast, a German study concluded that the suicide rate was not increased compared to the general population (Eicher, 1992). To the best of our knowledge, no study correlated sex hormone status or spermatogenic level with psychological and physiological outcomes during CHT, neither before nor after SRS.

SIDE EFFECTS OF CHT AND CONTROL EXAMINATIONS

It is recommended that transgender individuals undergoing CHT are checked initially every 3 months and then at least annually for hematological changes liver and kidney function and blood pressure during the first year and then every 6–12 months from the second year onwards (Meriggiola & Berra, 2013). No deaths, cardiovascular events, osteoporotic fractures, venous thromboses, or pulmonary embolisms were observed in trans-women (Wierckx *et al.*, 2014b).

We found a pronounced increase in prolactin in male-to-female subjects on the day of SRS (Schneider *et al.*, 2015). The elevated levels of prolactin (greater than 1000 mU/L) were associated with high doses of estrogens and advanced age at the start of the treatment (Asscheman *et al.*, 1988). Prolactinomas in male-to-female transsexual subjects due to high and conventional doses of estrogens have been reported (Asscheman *et al.*, 1988; Cunha *et al.*, 2015), but the clinical relevance of increased prolactin levels during CHT remains unknown (Wierckx *et al.*, 2014b).

Dual-energy X-ray absorptiometry is recommended in patients at risk for developing osteoporosis (i.e. family history) and at an advanced age (>60 years; (Meriggiola & Berra, 2013). It was shown that 20.5% of the follow-up patients suffered from osteopenia and 7.7% were diagnosed with osteoporosis (Judge *et al.*, 2014). Estrogens (in combination with anti-androgens) decrease bone turnover, with a subsequent increase in bone marrow density and a decrease in serum Insulin like growth hormone 1 (van Kesteren *et al.*, 1996). Bone loss may occur despite estrogen supplementation due to the effects of anti-androgens,

which lower testosterone serum concentrations and induce hypogonadism (Meriggiola & Berra, 2013). Although there is no evidence that prostate cancer is more frequent in GD patients, the prostate should be monitored from the age of 50 onwards, as generally recommended for men (Gooren & Morgentaler, 2014).

PROBLEMATIC ASPECTS IN RELATION TO SEX REASSIGNMENT TREATMENT

It appears obvious that maintenance of steroid hormone levels in the physiological range of the desired sex should be achieved in individuals with GD prior and post-SRS (Meriggiola *et al.*, 2010). The Endocrine Society recommends monitoring patients every 3 months during the first year of therapy and once or twice yearly thereafter (Hembree *et al.*, 2009). For CHT to be well tolerated, it is necessary to perform the hormonal administration in a highly individualized scheme in terms of timing, doses and modes of administration (Meriggiola & Berra, 2013). Treatment can be considered successful if it relieves distress or facilitates substantial improvement in function and well-being of the patient (Byne *et al.*, 2012).

The hormonal therapy in MtF subjects lasts 6.0 years on average (Wierckx *et al.*, 2014b). Based on expert opinion, however, patients tend to follow their self-controlled individual regimes as estrogen- and androgen-formulations are easily available via the Internet, over the counter, without prescription in certain settings, and through veterinary supply (Byne *et al.*, 2012). However, subjects should be strongly discouraged from inducing supra-physiological hormone levels due to serious side effects (Meriggiola & Berra, 2013). According to Leinung *et al.* (2013), 9.8% of male-to-female transsexuals started hormonal therapy without prescriptions from a physician and nearly all admitted of initiating hormonal therapy without medical supervision (Leinung *et al.*, 2013). This is surprising as one of the three inclusion criteria of the WPATH for GD therapy is the ability to take hormones in a responsible manner (WPATH, 2011).

Before starting CHT, it is indicated to inform the patient about contraceptive needs during CHT. Also, patients should be counseled about options of fertility preservation by cryopreservation of semen (Byne *et al.*, 2012). The desire to reproduce and raise children is an inadequately studied field in transsexual persons. It is known that masturbation can be emotionally challenging and cryopreservation might also be a financial burden for GD patients (De Sutter, 2001; Wierckx *et al.*, 2012). Yet, cryopreservation of spermatozoa, which can be used later for insemination —in vitro fertilization (IVF) or intracytoplasmatic sperm injection (ICSI), is a validated approach (T'Sjoen *et al.*, 2013). Moreover, spermatozoa from testicular tissue can be preserved after retrieval by biopsy or—when the involution is not fully complete - from the dissected testes or epididymides following SRS, as only few spermatozoa are needed to attain fertilization and pregnancy through ICSI with cryopreserved testicular or epididymal spermatozoa (T'Sjoen *et al.*, 2013).

Moreover, transgender medicine is rarely part of medical school curricula (Safer & Pearce, 2013), even though introduction of modules early during clinical education was suggested (Wylie *et al.*, 2016). One of the consequences of non-adequate staff training is that individuals suffering from GD are ignored and often dismissed in healthcare settings (Fabris *et al.* 2015). An interdisciplinary approach including several specialists will be mandatory for the adequate care of these patients (Fig. 1).

CONCLUSION

Adequate hormonal treatment in male-to-female GD patients is undoubtedly beneficial and is associated with higher social, emotional, and mental quality of life scores (Gorin-Lazard *et al.*, 2012). However, the treatment of transsexual subjects is a challenging task. In collaboration with mental health professionals and surgeons, endocrinologists are asked to confirm the diagnosis and individually adjust hormonal treatments with the goal to adequately suppress endogenous sex hormone levels and to achieve and maintain hormone characteristics of the desired gender (Meriggiola *et al.*, 2010).

Sex reassignment therapy with CHT and SRS has a major impact on the psychology and physiology of individual patients. Research has shown that patients on the day of SRS are very different regarding hormonal status ranging from feminized to virilized sex hormone levels. In addition, the status of spermatogenesis ranges from intact spermatogenesis to complete atrophy, irrespective of sex hormone levels. Patients with virilized hormone levels and complete spermatogenesis could face problems adjusting after SRS due to the sudden withdrawal of testosterone. Patients from our own studies were highly variable at the time of SRS.

Based on the literature review and based on our own research, we recommend a sufficient anti-androgen therapy with CPA (100 mg daily) or GnRH analogues (3.75 mg monthly) in addition to favorable estrogen replacement therapy depending on the individual patient until the day of SRS and under close supervision of an experienced endocrinologist (Fig. 1). Furthermore, estrogen treatment should be continued after SRS to prevent hypogonadism (Meriggiola *et al.* 2015). In order to achieve a better standardization of treatment results, including the effect on spermatogenesis, a higher standardization of treatment protocols appears to be essential. We therefore propose monitoring of sex hormones (LH, FSH, testosterone, free testosterone, prolactin, estrogen, SHBG) during CHT as well as after SRS and monitoring of the testicular status (i.e. testicular weight, ejaculate examination) prior to SRS on an annual basis. Based on these parameters, treatment protocols can then be further refined in the future studies. We also suggest discussing fertility options and contraceptive strategies during the course of CHT until SRS. Finally, health personal needs to be trained to improve and develop individual care strategies for transgender patients.

REFERENCES

American Psychiatric Association. (2013) *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. American Psychiatric Publishing, Arlington, VA.

Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G & Fernandez-Aranda F. (2015) Systematic review and meta-analysis of prevalence studies in transsexualism. *Eur Psychiatry* 30, 807–815.

Asscheman H, Gooren LJ, Assies J, Smits JP & de Slegte R. (1988) Prolactin levels and pituitary enlargement in hormone-treated male-to-female transsexuals. *Clin Endocrinol (Oxf)* 28, 583–588.

Bremner WJ. (2012) Contraception for men: a breakthrough new approach. *Cell* 150, 667–668.

Bunck MC, Debono M, Giltay EJ, Verheijen AT, Diamant M & Gooren LJ. (2009) Autonomous prolactin secretion in two male-to-female transgender patients using conventional oestrogen dosages. *BMJ Case Rep*, 2009, pii: bcr02.2009.1589.

Byne W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HF, Pleak RR, Tompkins DA; American Psychiatric

Association Task Force on Treatment of Gender Identity Disorder. (2012) Report of the american psychiatric association task force on treatment of gender identity disorder. *Arch Sex Behav* 41, 759–796.

Cunha FS, Domenice S, Camara VL, Sircili MH, Gooren LJ, Mendonca BB & Costa EM. (2015) Diagnosis of prolactinoma in two male-to-female transsexual subjects following high-dose cross-sex hormone therapy. *Andrologia* 47, 680–684.

De Sutter P. (2001) Gender reassignment and assisted reproduction: present and future reproductive options for transsexual people. *Hum Reprod* 16, 612–614.

Dhejne C, Lichtenstein P, Boman M, Johansson AL, Langstrom N & Landen M. (2011) Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS ONE* 6, e16885.

Eicher W. (1992) *Transsexualismus: Möglichkeiten und Grenzen der Geschlechtsumwandlung*. Gustav Fischer Verlag, Stuttgart.

Elbers JM, Asscheman H, Seidell JC, Frolich M, Meinders AE & Gooren LJ. (1997) Reversal of the sex difference in serum leptin levels upon cross-sex hormone administration in transsexuals. *J Clin Endocrinol Metab* 82, 3267–3270.

Fabris B, Bernardi S & Trombetta C. (2015) Cross-sex hormone therapy for gender dysphoria. *J Endocrinol Invest* 38, 269–282.

Fisher AD, Castellini G, Bandini E, Casale H, Fanni E, Benni L, Ferruccio N, Meriggiola MC, Manieri C, Gualerzi A, Jannini E, Oppo A, Ricca V, Maggi M & Rellini AH. (2014) Cross-sex hormonal treatment and body uneasiness in individuals with gender dysphoria. *J Sex Med* 11, 709–719.

Fisher AD, Ristori J, Fanni E, Castellini G, Forti G & Maggi M. (2016) Gender identity, gender assignment and reassignment in individuals with disorders of sex development: a major of dilemma. *J Endocinol Invest* 39, 1207–1224.

Fogh M, Corker CS, Hunter WM, McLean H, Philip J, Schon G & Skakkebaek NE. (1979) The effects of low doses of cyproterone acetate on some functions of the reproductive system in normal men. *Acta Endocrinol* 91, 545.

Fuss J, Hellweg R, Van Caenegem E, Briken P, Stalla GK, T'Sjoen G & Auer MK. (2015) Cross-sex hormone treatment in male-to-female transsexual persons reduces serum brain-derived neurotrophic factor (BDNF). *Eur Neuropsychopharmacol* 25, 95–99.

Giltay EJ & Gooren LJ. (2000) Effects of sex steroid deprivation/administration on hair growth and skin sebum production in transsexual males and females. *J Clin Endocrinol Metab* 85, 2913–2921.

Gooren LJ. (2011) Clinical practice. Care of transsexual persons. *N Engl J Med* 364, 1251–1257.

Gooren LJ & Morgentaler A. (2014) Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia* 46, 1156–1160.

Gooren LJ, Giltay EJ & Bunck MC. (2008) Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 93, 19–25.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebleux S, Penochet JC, Pringuey D, Albarel F, Morange I, Loundou A, Berbis J, Auquier P, Lancon C & Bonierbale M. (2012) Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study *J Sex Med* 9, 531–541.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ, Spack NP, Tangpricha V, Montori VM; Endocrine Society. (2009) Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*, 94(9), 3132–3154.

Hess J, Rossi R, Panic L, Rübben H & Senf W. (2014) Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int* 111, 795–801.

Heylens G, Verroken C, De Cock C, T'Sjoen G & De Cuypere G. (2014) Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med* 11, 119–126.

Judge C, O'Donovan C, Callaghan G, Gaoatswe G & O'Shea D. (2014) Gender dysphoria - prevalence and co-morbidities in an irish adult population. *Front Endocrinol (Lausanne)* 5, 87.

van Kesteren P, Lips P, Deville W, Popp-Snijders C, Asscheman H, Megens J & Gooren LJ. (1996) The effect of one-year cross-sex hormonal treatment on bone metabolism and serum insulin-like growth factor-1 in transsexuals. *J Clin Endocrinol Metab* 81, 2227–2232.

van Kesteren PJ, Asscheman H, Megens JA & Gooren LJ. (1997) Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)* 47, 337–342.

Kisman OK, de Voogt HJ & Baak JA. (1990) Reversibility of the effect of LHRH agonists and other antiandrogenic hormones on the testis: a histomorphometric study. *Eur Urol* 18, 299–301.

Kuyper L & Wijsen C. (2014) Gender identities and gender dysphoria in the Netherlands. *Arch Sex Behav* 43, 377–385.

Labrie F, Belanger A, Luu-The V, Labrie C, Simard J, Cusan L, Gomez J & Candas B. (2005) Gonadotropin-releasing hormone agonists in the treatment of prostate cancer. *Endocr Rev* 26, 361–379.

Leinung MC, Urizar MF, Patel N & Sood SC. (2013) Endocrine treatment of transsexual persons: extensive personal experience. *Endocr Pract* 19, 644–650.

Liu PY, Swerdloff RS, Christenson PD, Handelsmann DJ, Wang C; Hormonal Male Contraception Summit. (2006) Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. *Lancet*, 367(9520), 1412–1420.

Lu CC & Steinberger A. (1978) Effects of estrogen on human seminiferous tubules: light and electron microscopic analysis. *Am J Anat* 153, 1–13.

Lubbert H, Leo-Rossberg I & Hammerstein J. (1992) Effects of ethinyl estradiol on semen quality and various hormonal parameters in a eugonadal male. *Fertil Steril* 58, 603–608.

Mayerhofer A. (2013) Human testicular peritubular cells: more than meets the eye". *Reproduction* 145, R107–R116.

Meriggiola MC & Berra M. (2013) Safety of hormonal treatment in transgenders. *Curr Opin Endocrinol Diabetes Obes* 20, 565–569.

Meriggiola MC & Gava G. (2015) Endocrine care of transpeople part II. A review of cross-sex hormone treatment, outcomes and adverse effects in transwomen. *Clin Endocrinol (Oxf)* 83, 607–615.

Meriggiola MC, Bremner WJ, Costantino A, Di Cintio G & Flamigni C. (1998) Low dose of cyproterone acetate and testosterone enanthate for contraception in men. *Hum Reprod* 13, 1225–1229.

Meriggiola MC, Jannini EA, Lenzi A, Maggi M & Manieri C. (2010) Endocrine treatment of transsexual persons: an Endocrine Society Clinical Practice Guideline: commentary from a European perspective. *Eur J Endocrinol* 162, 831–833.

Moltz L, Römmler A, Post K, Schwartz U & Hammerstein J. (1980) Medium dose cyproterone acetate (CPA): effects on hormone secretion and on spermatogenesis in man. *Contraception* 21, 393.

Nieschlag E, Kamischke A & Behre HM. (2004) Hormonal male contraception: the essential role of testosterone. In: *Testosterone: Action, Deficiency, Substitution*, 3rd edn (eds E Nieschlag & HM Behre), pp. 685-714. Cambridge University Press, Cambridge, UK.

Payer AF, Meyer WJ & Walker PA. (1979) The ultrastructural response of human Leydig cells to exogenous estrogens. *Andrologia* 11, 423–436.

Plant TM, Ramaswamy S, Simorangkir D & Marshall GR. (2005) Postnatal and pubertal development of the rhesus monkey (Macaca mulatta) testis. *Ann N Y Acad Sci* 1061, 149–162.

Rodriguez-Rigau LJ, Tcholakian RK, Smith KD & Steinberger E. (1977) In vitro steroid metabolic studies in human testes. II: metabolism of cholesterol, pregnenolone, progesterone, androstenedione and testosterone by testes of an estrogen-treated man. *Steroids* 30, 729–739.

Safer JD & Pearce EN. (2013) A simple curriculum content change increased medical student comfort with transgender medicine. *Endocr Pract* 19, 633–637.

Sapino A, Pagani A, Godano A & Bussolati G. (1987) Effects of estrogens on the testis of transsexuals: a pathological and immunocytochemical study. *Virchows Arch A Pathol Anat Histopathol* 411, 409–414.

Schagen S, Cohen-Kettenis P, Delemarre-van de Waal H & Hannema S. (2016) Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents. *J Sex Med* 13, 1125–1132.

Schneider F, Neuhaus N, Wistuba J, Zitzmann M, Hess J, Mahler D, von Ahlen H, St Schlatt & Kliesch S. (2015) Testicular functions and clinical characterization of patients with gender dysphoria (GD) undergoing sex reassignment surgery (SRS). *J Sex Med* 12, 2190–2200.

Schulze C. (1988) Response of the human testis to long-term estrogen treatment: morphology of Sertoli cells, Leydig cells and spermatogonial stem cells. *Cell Tissue Res* 251, 31–43.

Thiagaraj D, Gunasegaram R, Loganath A, Peh KL, Kottegoda SR & Ratnam SS. (1987) Histopathology of the testes from male transsexuals on oestrogen therapy. *Ann Acad Med Singapore* 16, 347–348.

T'Sjoen G, Van Caenegem E & Wierckx K. (2013) Transgenderism and reproduction. *Curr Opin Endocrinol Diabetes Obes* 20, 575–579.

Turner D, Basdekis-Jozsa R & Briken P. (2013) Prescription of testosterone-lowering medications for sex offender treatment in German forensic-psychiatric institutions. *J Sex Med* 10, 570–578.

Unger CA. (2014) Care of the transgender patient: the role of the gynecologist. *Am J Obstet Gynecol* 210, 16–26.

Venizelos ID & Paradinas FJ. (1988) Testicular atrophy after oestrogen therapy. *Histopathology* 12, 451–454.

Wang C & Yeung KK. (1980) Use of low-dosage oral cyproterone acetate as a male contraceptive. *Contraception* 21, 245–272.

Wierckx K, Van Caenegem E, Elaut E, Dedecker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G & T'Sjoen G. (2011) Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med* 8, 3379–3388.

Wierckx K, Stuyver I, Weyers S, Hamada A, Agarwal A, De Sutter P & T'Sjoen G. (2012) Sperm freezing in transsexual women. *Arch Sex Behav* 41, 1069–1071.

Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, Weyers S, Hoebeke P & T'Sjoen G. (2014a) Sexual desire in trans persons: associations with sex reassignment treatment. *J Sex Med* 11, 107–118.

Wierckx K, Van Caenegem E, Schreiner T, Haraldsen I, Fisher A, Toye K, Kaufman JM & T'Sjoen G. (2014b) Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. *J Sex Med* 11, 1999–2011.

WPATH (2011) The Standards of Care WPATH Version 7. Retrieved 26th of January 2014, 2014

Wylie K, Knudson G, Khan SI, Bonierbale M, Watanyusakul S & Baral S. (2016) Serving transgender people: clinical care considerations and service delivery models in transgender health. *Lancet* 388, 401–411.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Important diagnostic references for diagnosing and treating gender dysphoria patients: (A) Diagnosis according to Diagnostic and Statistical Manual of Mental Disorders (DSM V), (B) Criteria of the World Professional Association of Transgender Health (WPATH) before starting CHT, (C) Multidisciplinary treatment according to the European guidelines of the Endocrine Society and (D) eligible criteria for SRS according to the European guidelines of the Endocrine Society.

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human reproduction ORIGINAL ARTICLE *Reproductive biology*

Histological study on the influence of puberty suppression and hormonal treatment on developing germ cells in transgender women

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STUDY QUESTION: Can transgender women cryopreserve germ cells obtained from their orchiectomy specimen for fertility preservation, after having used puberty suppression and/or hormonal treatment?

SUMMARY ANSWER: In the vast majority of transgender women, there were still immature germ cells present in the orchiectomy specimen, and in 4.7% of transgender women—who all initiated medical treatment in Tanner stage 4 or higher—mature spermatozoa were found, which would enable cryopreservation of spermatozoa or testicular tissue after having used puberty suppression and/or hormonal treatment.

WHAT IS KNOWN ALREADY: Gender affirming treatment (i.e. puberty suppression, hormonal treatment, and subsequent orchiectomy) impairs reproductive function in transgender women. Although semen cryopreservation is generally offered during the transition process, this option is not feasible for all transgender women (e.g. due to incomplete spermatogenesis when initiating treatment in early puberty, in case of inability to masturbate, or when temporary cessation of hormonal treatment is too disruptive). Harvesting mature spermatozoa, or testicular tissue harboring immature germ cells, from orchiectomy specimens obtained during genital gender-affirming surgery (gGAS) might give this group a chance of having biological children later in life. Previous studies on spermatogenesis in orchiectomy specimens showed conflicting results, ranging from complete absence of germ cells to full spermatogenesis, and did not involve transgender women who initiated medical treatment in early- or late puberty.

STUDY DESIGN, SIZE, DURATION: Histological and immunohistochemical analyses were performed on orchiectomy specimens from 214 transgender women who underwent gGAS between 2006 and 2018. Six subgroups were identified, depending on pubertal stage at initiation of medical treatment (Tanner stage 2-3, Tanner stage 4-5, adult), and whether hormonal treatment was continued or temporarily stopped prior to gGAS in each of these groups.

PARTICIPANTS/MATERIALS, SETTING, METHODS: All transgender women used a combination of estrogens and testosterone suppressing therapy. Orchiectomy specimen sections were stained with Mayer's hematoxylin and eosin and histologically analyzed to assess the Johnsen score and the ratio of most advanced germ cell types in at least 50 seminiferous tubular cross-sections. Subsequently, immunohistochemistry was used to validate these findings using spermatogonia, spermatocytes or spermatids markers (MAGE-A3/A4, γH2AX, Acrosin, respectively). Possibilities for fertility preservation were defined as: preservation of spermatozoa, preservation of spermatogonial

stem cells or no possibilities (in case no germ cells were found). Outcomes were compared between subgroups and logistic regression analyses were used to assess the association between the duration of hormonal treatment and the possibilities for fertility preservation.

MAIN RESULTS AND THE ROLE OF CHANCE: Mature spermatozoa were encountered in 4.7% of orchiectomy specimens, all from transgender women who had initiated medical treatment in Tanner stage 4 or higher. In 88.3% of the study sample orchiectomy specimens only contained immature germ cells (round spermatids, spermatocytes or spermatogonia, as most advanced germ cell type). In 7.0%, a complete absence of germ cells was observed, all these samples were from transgender women who had initiated medical treatment in adulthood. Cessation of hormonal treatment prior to gGAS did not affect the presence of germ cells or their maturation stage, nor was there an effect of the duration of hormonal treatment prior to gGAS.

LIMITATIONS, REASONS FOR CAUTION: Since data on serum hormone levels on the day of gGAS were not available, we were unable to verify if the transgender women who were asked to temporarily stop hormonal treatment 4 weeks prior to surgery actually did so, and if people with full spermatogenesis were compliant to treatment.

WIDER IMPLICATIONS OF THE FINDINGS: There may still be options for fertility preservation in orchiectomy specimens obtained during gGAS since a small percentage of transgender women had full spermatogenesis, which could enable cryopreservation of mature spermatozoa via a testicular sperm extraction procedure. Furthermore, the vast majority still had immature germ cells, which could enable cryopreservation of testicular tissue harboring spermatogonial stem cells. If maturation techniques like *in vitro* spermatogenesis become available in the future, harvesting germ cells from orchiectomy specimens might be a promising option for those who are otherwise unable to have biological children.

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Key words: transgender women / orchiectomy / fertility preservation / testicular tissue / spermatogenesis / hormonal treatment / azoospermia / germ cells

Introduction

Gender dysphoria refers to the distress experienced by people with an incongruence between their sex assigned at birth and their gender identity (APA, 2013). People assigned male at birth with a female gender identity are referred to as transgender women.

Many transgender women seek medical treatment to avoid (further) masculinization and induce feminization, and hereby align their physical characteristics with their gender identity. The preferred treatment protocol depends on the person's age at time of start of medical treatment. For adolescents (<18 years), treatment can be initiated when a person reaches puberty (Tanner stage 2 or higher, determined by the development of secondary sex characteristics). It aims to suppress further pubertal development by administration of a gonadotropin-releasing hormone agonist (GnRHa) which reversibly inhibits the production of sex hormones. Hereby, adolescents have more time to explore options and to live in the experienced gender before deciding whether or not to proceed with additional, sometimes irreversible, treatments. At the age of approximately 16 years, treatment can be supplemented with estrogens to induce the development of female secondary sex characteristics (Hembree *et al.*, 2017). For transgender women presenting at adult age (≥18 years), treatment usually does not consist of a phase of hormone suppression only, but immediately involves a combination of anti-androgens and estrogens, to achieve feminization. The combination of testosterone suppressing therapy and estrogen supplementation is referred to as gender affirming hormonal treatment (GAHT). Transgender women of 18 years or older who have used GAHT for at least one year, can opt for genital gender-affirming surgery (gGAS) if no surgical contraindications are present. gGAS may comprise vaginoplasty, gender confirming vulvoplasty or bilateral orchiectomy, depending on the desires of the individual (van der Sluis *et al.*, 2021).

The use of testosterone suppressing therapy results in a severely impaired reproductive function, since spermatogenesis—the differentiation of spermatogonial stem cells into spermatozoa—requires adequate levels of intratesticular testosterone (Adeleye *et al.*, 2019). This reproductive loss is permanent after gGAS. Although gender affirming treatment significantly improves quality of life, reproductive loss may be an unwanted consequence (Auer *et al.*, 2018; Chen *et al.*, 2018; Vyas *et al.*, 2020). Therefore, it is important that (future) desire for biological children and the options for fertility preservation are discussed and offered prior to the start of medical treatment (Hembree *et al.*, 2017).

The currently available option for fertility preservation in transgender women is cryopreservation of spermatozoa from a semen sample, obtained through ejaculation. Cryopreservation of surgically obtained spermatozoa through testicular sperm extraction (TESE) may serve as an alternative for those who are unable to ejaculate or in case of azoospermia (Wallace *et al.*, 2014).

A complicating factor for contemporary fertility preservation in transgender female adolescents is the requirement of complete spermatogenesis, which only develops from Tanner stage 3 onwards, under the influence of increasing intratesticular testosterone levels. If puberty suppression is started in Tanner stage 2, full spermatogenesis is usually not present yet and therefore preservation of spermatozoa is not possible (Brik *et al.*, 2019). The equipoise of commencing medical treatment to avoid progression of puberty and delaying treatment to enable semen cryopreservation as only option for biological children may be stressful, as puberty is accompanied by irreversible and often unwanted physical changes such as a lowering of the voice and facial hair growth. Severe genital dysphoria may pose another barrier for fertility preservation, since semen cryopreservation requires masturbation which is non-negotiable for some young transgender women (Brik *et al.*, 2019). In addition, TESE, the currently available alternative to

obtain spermatozoa for cryopreservation requires invasive procedures including surgery and (general) anesthesia.

For transgender women, cryopreservation of germ cells harvested from testicular tissue obtained during gGAS may serve as an alternative to keep the option for genetically related offspring open. How these germ cells can be used for procreation depends on their maturation phase. Spermatozoa can directly be used for ART. However, the use of immature germ cells relies on the feasibility of maturation techniques outside the human body, such as *in vitro* spermatogenesis. Unfortunately, complete *in vitro* spermatogenesis has only been successfully demonstrated in mouse models and is still unsuccessful in humans (Sato *et al.*, 2011). If *in vitro* spermatogenesis becomes available in the future, cryopreservation of testicular tissue containing spermatogonial stem cells might be a promising option for fertility preservation in those who are otherwise unable to retain the possibility of having genetically related offspring.

Currently, limited data are available on the effect of GAHT on testicular histology and the most advanced germ cell type that can be harvested from testicular tissue obtained at time of gGAS. Previous studies conducted on this topic showed varying proportions of hyalinization of seminiferous tubules as well as conflicting results regarding spermatogenesis, ranging from a complete absence of germ cells to full spermatogenesis (Schneider *et al.*, 2017; Matoso *et al.*, 2018). Moreover, none of these studies focused on people who initiated medical treatment in early puberty.

The primary aim of this study is to evaluate the influence of puberty suppression and/or GAHT on exocrine testicular function, by determining the most advanced germ cell type in orchiectomy specimens obtained during gGAS. We aim to compare the outcome between people who started medical treatment as adult (≥18 years) and those who started as adolescent in early puberty (Tanner stage 2-3) or late puberty (Tanner stage 4-5). In addition, we will assess the influence of discontinuation of medical treatment 4 weeks prior to gGAS in each of these groups, and the association between the duration of hormonal treatment and the possibilities for fertility preservation. Hereby, we will get insights in the options for fertility preservation in orchiectomy specimens obtained during gGAS after having used puberty suppression and/or hormonal treatment.

Materials and methods

Study population and clinical data collection

For this study, we used orchiectomy specimens of transgender women who underwent bilateral orchiectomy combined with vaginoplasty at the Center of Expertise on Gender Dysphoria of Amsterdam UMC between 2006 and 2019. All participants provided written permission for the use of their body material and clinical data for research purposes. The Ethical Review Board of the Amsterdam UMC, location VUMC provided approval for conducting this study (METC2014322).

A total of 788 transgender women were identified. Data on medical history, age and Tanner stage at start of medical treatment, documented hormone use, date of gGAS, alcohol consumption, smoking, drug use, BMI at time of gGAS and last known serum hormone levels before gGAS, were collected from the medical files. Transgender women were categorized according to age and Tanner stage at initiation of medical treatment (Tanner stage 2-3, Tanner stage 4-5 or ≥18 years). Transgender women operated before 2017 discontinued GAHT 4 weeks prior to surgery, because of a presumed increased risk of perioperative thrombosis. As evidence suggested this risk is negligible, GAHT is continued in the perioperative period since July 2017. Six subgroups were created based on Tanner stage/age at start of medical treatment and continuation/discontinuation of GAHT prior to gGAS. People with an unknown age or Tanner stage at time of initiation of medical treatment were excluded. Other exclusion criteria were hard drug use, cryptorchidism, a medical history of receiving chemotherapy or genetic disorders which can all possibly impair spermatogenesis. Lastly, since the vast majority used estrogens combined with either triptorelin, or cyproterone acetate, people who used estrogen monotherapy and those who used spironolactone as anti-androgenic treatment were excluded to create a homogeneous study population. A maximum number of 80 transgender women were enrolled per group as this was deemed sufficient to answer the study questions. A random sample was drawn from groups that exceeded 80 individuals using STATA Statistical Software, version 15.1 (Statacorp, College Station, TX, USA). In total, 263 transgender women were selected for inclusion in the study cohort.

Testicular tissue preparation and analysis

Preparation for histology

Testicular tissue was obtained from the biobank of the Pathology Department of Amsterdam UMC, where orchiectomy specimens, obtained during gGAS, were stored after histopathological analysis for clinical purposes. Upon arrival at the Pathology Department, the orchiectomy specimens were fixed in 4% w/v paraformaldehyde and embedded in paraffin. For this study, seven slices of 5 µm thickness of one testicle were sectioned and mounted on microscope slides. From one slide of each specimen paraffin sections were deparaffinized and subsequently stained with Mayer's hematoxylin and eosin, and at least one other slide was used for immunohistochemistry to confirm germ cell subtypes.

Histological analysis

Histological examination was conducted using a bright field microscope (Olympus BX41, OM Digital Solutions Americas, Bethlehem, PA, USA). From each specimen, at least 50 seminiferous tubules per slide were analyzed to assess spermatogenesis by determining the most advanced germ cell type from each seminiferous tubular cross-section based on their location within the tubule and nuclear morphology. The Modified Johnsen's scoring system was used to assign a score to each tubule, and per slide a mean Johnsen's score was calculated. The Modified Johnsen's scoring system involves a 10-point Likert scale where score 1 corresponds to complete sclerosis without recognizable seminiferous epithelium, and score 10 implies the presence of more than 10 elongated spermatids without immature and apoptotic cells in the lumen (Supplementary Table SI) (Johnsen, 1970).

After assessment of spermatogenesis, overall testicular histology was assessed including the presence of a lumen in the seminiferous tubules and rate of seminiferous tubule hyalinization. The lumen was categorized as open, half-open or absent. Hyalinization was defined as a

hyaline area separating the peritubular layer from the basal membrane of the seminiferous tubule.

Preparation for immunohistochemistry

In order to validate our findings, a second slide of each specimen was analyzed using immunohistochemistry. The primary antibodies were chosen based on the most advanced germ cell type that was identified during histological analysis, or on uncertainty regarding the presence of a germ cell type.

For the detection of spermatogonia, slides were stained for spermatogonial marker MAGE-A3/A4 using mouse monoclonal Anti-Mage A3/A4 antibody (clone 57B; Merck Millipore, Germany). Endogenous peroxidase activity was inactivated with 0.3% H_2O_2/phosphate-buffered saline (PBS) for 10 min at room temperature in the dark. Non-specific binding sites were then blocked with Superblock (ScyTek Lab, USA) for 1 h at room temperature in a humid slide box. Sections were subsequently incubated overnight at 4°C with Anti-Mage A3/A4 antibody diluted 1:2000 in BrightDiluent (Immunologic, the Netherlands). The next day, all slides were washed three times with PBS followed by 30 min incubation with Powervision goat-anti Mouse/Rabbit poly-horseradish peroxidase (DPVO110HRP, Immunologic, the Netherlands) secondary antibody at room temperature. After washing, the signal was visualized using Bright-DAB (3,3′-diaminobenzidine, Immunologic, the Netherlands) after which the sections were counterstained with Mayer's hematoxylin. Finally, after dehydration in increasing ethanol concentrations and xylene, the slides were encapsulated with glass coverslips using Entellan® (Merck Millipore, Germany) for further microscopic analysis.

For the detection of spermatocytes, slides were stained for γH2AX using mouse monoclonal Anti-phospho-Histone H2A.X (Merck Millipore, Germany) antibody. Antigen retrieval was carried out by boiling tissue sections in Tris-EDTA buffer (10 mM Tris, 1 mM EDTA, pH = 9.0). The buffer was first heated until boiling in the microwave for 3 min at maximum Watt. After cooling down for 2 min at room temperature, the buffer was heated again in the microwave for 12 min at minimum Watt. Non-specific binding sites were blocked with 5% bovine serum albumin (BSA)/PBS/0.5% Triton X-100. This was followed by overnight incubation at 4°C with Anti-phospho-Histone H2A.X diluted 1:150 in 1% BSA/PBS/0.05% Tween. After incubation of the primary antibody, the same steps were performed as for the detection of spermatogonia with MAGE-A3/A4.

For the detection of round spermatids and spermatozoa, slides were stained for the presence of their Acrosin cap using rabbit polyclonal Acrosin antibody (ThermoFisher, PA5-61804). Antigen retrieval was carried out by boiling tissue sections in 0.01 M sodium citrate buffer (tri-sodium citrate dihydrate $Na_3C_6H_5O_7.2H_2O$, pH 6.0). The buffer was first heated until boiling in the microwave for 3 min at maximum Watt. After cooling down for 2 min at room temperature, the buffer was heated again in the microwave for 10 min at minimum Watt. Subsequently, the buffer was cooled down for 10 min at room temperature and placed under running tap water. After these steps, a standard immunohistochemical preparation protocol was followed, as described above.

For all three antibodies, slides with testicular tissue from a prostate cancer patient with normal spermatogenesis served as a positive control. Negative controls were carried out by replacing the first antibody by isotype IgG (Supplementary Fig. S1).

Immunohistochemical analysis

The immunohistochemically stained slides were examined using a bright field microscope (Olympus BX41) and assessed on the presence of the specifically targeted germ cell type. Outcome was then used to validate the Modified Johnsen's scoring of the histologically analyzed slide of that same specimen. Results from the immunohistochemically stained slides were preferred if there was a difference between the two.

Statistical analyses

After completion of histological and immunohistochemical analyses, results were linked to clinical data and descriptive analyses were conducted for the total cohort and the six subgroups. Data are presented as means (SD) when normally distributed, as medians with interquartile ranges (IQRs) when non-normally distributed, or as numbers with percentage.

Progress of spermatogenesis, determined by the presence of the most advanced germ cell type per orchiectomy specimen, was used as main outcome measurement (no germ cells, spermatogonia, spermatocytes, round spermatids or spermatozoa). Secondary outcome measurements included mean Johnsen score per orchiectomy specimen, the degree of hyalinization and presence of a lumen.

To assess the possibilities for fertility preservation three categories were defined: preservation of spermatozoa; preservation of spermatogonial stem cells for those with round spermatids, spermatocytes or spermatogonia as most advanced germ cell type; and no possibilities for those with a complete absence of germ cells. Outcome was expressed as proportion with 95% confidence interval (95% CI) and compared between people who started medical treatment as an adult (>18 years) and those who started as adolescent in early puberty (Tanner stage 2-3) or late puberty (Tanner stage 4-5) (Newcombe, 1998). Since some categories contained no observations, we were not able to perform statistical tests. Therefore, differences between groups are shown in a figure. To assess the effect of cessation of GAHT prior to surgery, Fisher's exact tests were used to compare outcome within each pubertal stage at initiation of medical treatment. The significance level was set at $P < 0.05$, and all tests were two-sided.

Lastly, logistic regression analyses were performed to assess the association between the duration of medical treatment and the possibility for preservation of spermatozoa, as well as the possibility for preservation of spermatogonial stem cells. Since the duration of medical treatment prior to gGAS, as well as progress of spermatogenesis both might be dependent on the age at start of medical treatment, a correction was performed for this factor. Odds ratios (ORs) with 95% CI were calculated.

All statistical analyses were performed using STATA Statistical Software, version 15.1 (Statacorp, College Station, TX, USA).

Results

Initially, 263 transgender women were selected for inclusion in the study cohort. A total of 35 individuals were excluded when, upon preparation for analysis of the orchiectomy specimens, it became evident that for these transgender women no tissue was stored at the Pathology department of Amsterdam UMC. Another 14 transgender

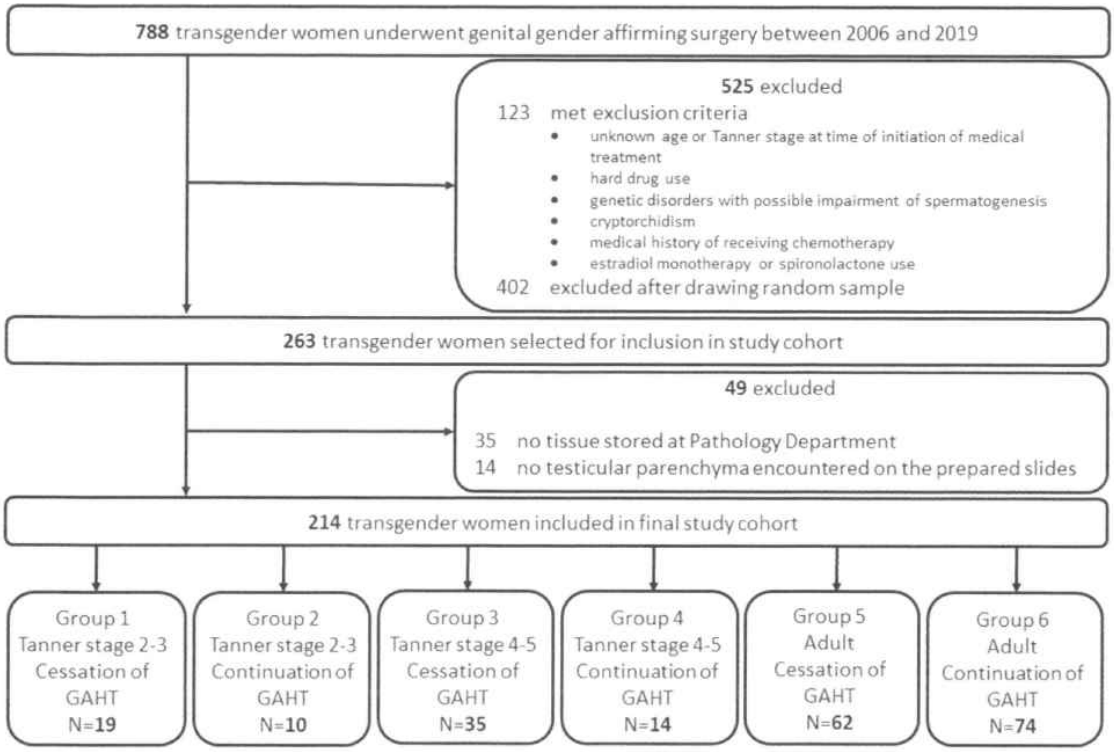

Figure 1. Study flowchart. GAHT, gender affirming hormonal treatment.

women were excluded because no testicular parenchyma was encountered on the prepared slides. Therefore, the final cohort consisted of 214 transgender women divided into 6 subgroups (Fig. 1).

Characteristics at time of gGAS are presented in Table I. Mean age at gGAS was 29.6 years (SD 12.4) and was lower in people who started medical treatment in adolescence compared to those who started medical treatment in adulthood. Since adolescents started medical treatment with puberty suppressive therapy and had to wait until reaching the age of 18 years before being able to undergo gGAS, prior medical treatment duration was longer in the adolescent subgroups compared to those who initiated treatment at adult age. Different estradiol formulations were prescribed, including estradiol patches (50–150 µg/24 h twice weekly), estradiol gel (0.75–3.0 mg daily) and oral estradiol valerate or hemihydrate (2–6 mg daily). Testosterone suppressing therapy consisted of triptorelin injections (3.75 mg i.m./s.c. every 4 weeks or 11.25 mg i.m. every 12 weeks) for those who initiated treatment as adolescent, and cyproterone acetate (25–100 mg daily) for those who initiated treatment as adult. The last known serum hormone levels, median 189 days (IQR 96–340) before gGAS, showed that testosterone was adequately suppressed (median 0.7 nmol/l, IQR 0.5–1.0) and estradiol levels were in the female range (median 193 pmol/l, IQR 120–307). Furthermore, LH and FSH levels were suppressed. In transgender women with a cessation of GAHT 4 weeks prior to gGAS, estradiol levels were lower and testosterone and LH levels were higher, compared to those who continued GAHT until gGAS.

In 10 transgender women (4.7%) some seminiferous tubules contained full spermatogenesis, all of whom had initiated medical treatment in Tanner stage 4 or higher and it occurred in both the group that had continued GAHT until gGAS and in the group that had discontinued four weeks prior to gGAS (Table II, Fig. 2E). Complete absence of germ cells was encountered in 15 transgender women (7.0%) (Fig. 2A), all of whom had initiated medical treatment in adulthood. Also, mean Johnsen's scores were lowest in the adult cohort. In the subgroup of transgender women who initiated medical treatment in Tanner stage 2 or 3, all specimens showed immature germ cells of which spermatogonia were most commonly observed (60–79%) (Fig. 2B–D). Supplementary Table SII shows the Modified Johnsen's score for each individual separately.

Hyalinization of seminiferous tubules was observed in 161 orchiectomy specimens (75.2%) and was most common in the adult subgroup (Fig. 3E and F). An open or half-open lumen of the seminiferous tubule was encountered in 8.4% and 25.2% of the orchiectomy specimens (Fig. 3A and B), respectively. The complete absence of a lumen was most common in those who initiated treatment in Tanner stage 2 or 3 (Fig. 3C).

Table 1 Baseline characteristics at time of genital gender affirming surgery (gGAS).

	Total (n = 214)	Adolescent Tanner stage 2-3 (n = 29)		Adolescent Tanner stage 4-5 (n = 49)		Adult (n = 136)	
		Cessation of GAHT (n = 19)	Continuation of GAHT (n = 10)	Cessation of GAHT (n = 35)	Continuation of GAHT (n = 14)	Cessation of GAHT (n = 62)	Continuation of GAHT (n = 74)
Age (years)—mean (SD)	29.6 (12.4)	19.0 (1.5)	19.6 (1.9)	19.7 (1.2)	19.3 (0.7)	34.5 (12.3)	36.2 (12.2)
Alcohol							
Drinker—% (n)	44 (82)	43 (6)	30 (3)	60 (18)	21 (3)	56 (26)	35 (26)
Non-drinker—% (n)	56 (106)	57 (8)	70 (7)	40 (12)	79 (11)	44 (20)	65 (48)
Unknown—n	26	5	0	5	0	16	0
Smoking							
Smoker—% (n)	7 (12)	0	0	8 (2)	0	22 (10)	0
Non-smoker—% (n)	93 (171)	100 (15)	100 (10)	92 (24)	100 (14)	78 (34)	100
Unknown—n	31	4	0	9	0	18	0
Cannabis use							
Yes—% (n)	3 (5)	0	0	4 (1)	7 (1)	6 (2)	1 (1)
No—% (n)	97 (166)	100 (15)	100 (10)	96 (24)	93 (13)	94 (31)	99 (73)
Unknown—n	43	4	0	10	0	29	0
BMI (kg/m^2)—mean (SD)	23.1 (3.3)	22.0 (3.3)	23.2 (2.8)	21.6 (3.6)	20.9 (3.6)	23.9 (2.9)	23.8 (3.0)
Mean duration of medical treatment (years)˜—(SD)	3.3 (2.0)	5.9 (1.4)	6.8 (1.3)	4.1 (1.8)	2.8 (0.6)	2.8 (1.9)	2.3 (1.2)
Testosterone suppression							
Triptorelin injections—% (n)	36 (78)	100 (19)	100 (10)	100 (35)	100 (14)	0	0
Cyproterone acetate—% (n)	64 (136)	0	0	0	0	100 (62)	100 (74)
Estrogen supplementation							
Transdermal formulation—% (n)	25 (54)	11 (2)	10 (1)	0	0	40 (25)	35 (26)
Oral formulation—% (n)	75 (160)	89 (17)	90 (9)	100 (35)	100 (14)	60 (37)	65 (48)
Serum hormone levels before gGAS—Median (IQR)^							
Testosterone (nmol/)	0.7 (0.5–1.0)	1.0 (0.8–1.0)	0.6 (0.5–0.8)	1.0 (0.6–1.2)	0.6 (0.5–1.1)	0.7 (0.5–1.0)	0.5 (0.5–0.8)
Estradiol (pmol/l)	193 (120–307)	95 (43–332)	160 (141–392)	120 (82–220)	222 (100–281)	219 (130–282)	237 (151–341)
LH (U/l)	0.1 (0.1–0.3)	0.2 (0.1–0.4)	0.3 (0.2–0.5)	0.3 (0.2–0.4)	0.2 (0.2–0.4)	0.1 (0.1–0.3)	0.1 (0.1–0.1)
FSH (U/l)	0.2 (0.1–0.5)	0.2 (0.1–0.5)	0.4 (0.4–0.5)	0.2 (0.1–0.5)	–	0.3 (0.1–0.5)	0.8 (0.1–3.0)

GAHT, gender affirming hormone treatment; IQR, interquartile range.
˜Including GnRH agonist use, if applicable.
^Data were available for 201 (testosterone and LH), 200 (estradiol), and 53 (FSH) transgender women, respectively.

When comparing the options for fertility preservation, we found that for some transgender women it would still have been possible to harvest mature spermatozoa from testicular tissue obtained during gGAS (Fig. 4). This was the case for 4% (95% CI 2–8) of the adult subgroup and 10% (95% CI 4–22) of adolescents in the Tanner stage 4-5 subgroup, compared to 0% in the Tanner stage 2-3 subgroup. For 100% of people in the Tanner stage 2-3 subgroup, 90% (95% CI 78–96) of people in the Tanner stage 4-5 subgroup and 85% (95% CI 78–90) of the adult subgroup, preservation of testicular tissue containing spermatogonial stem cells would have been their only option for fertility preservation. Furthermore, for 11% (95% CI 7–17) of the adult subgroup no options for fertility preservation would have been available, compared to 0% of the two adolescent subgroups. No statistically significant differences were found between those who had continued GAHT until gGAS and those with four weeks cessation of GAHT prior to gGAS.

Lastly, logistic regression analyses showed no association between the duration of GAHT and the possibility for preservation of spermatozoa (OR 0.75, 95% CI 0.47–1.18) or spermatogonial stem cells (OR 1.03, 95% CI 0.81–1.31).

Discussion

The results of our study imply that there may be options for fertility preservation for transgender women who are unable to pursue semen cryopreservation, by using testicular tissue from orchiectomy specimens obtained during gGAS. In a small percentage of transgender

Table II Results of histological and immunohistochemical analyses of orchiectomy specimens.

	Total (n = 214)	Adolescent Tanner stage 2–3 (n = 29)		Adolescent Tanner stage 4–5 (n = 49)		Adult (n = 136)	
		Cessation of GAHT (n = 19)	Continuation of GAHT (n = 10)	Cessation of GAHT (n = 35)	Continuation of GAHT (n = 14)	Cessation of GAHT (n = 62)	Continuation of GAHT (n = 74)
Spermatozoa	4.7 (10)	0 (0)	0 (0)	6 (2)	22 (3)	6 (4)	1 (1)
Round spermatids	0.5 (1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)
Spermatocytes	21.5 (46)	21 (4)	40 (4)	31 (11)	14 (2)	23 (14)	15 (11)
Spermatogonia	66.3 (142)	79 (15)	60 (6)	63 (22)	64 (9)	61 (38)	70 (52)
No germ cells	7.0 (15)	0 (0)	0 (0)	0 (0)	0 (0)	8 (5)	14 (10)
Mean Johnsen's score—(SD)	2.5 (0.8)	2.6 (0.3)	2.7 (0.4)	2.8 (0.8)	3.2 (1.4)	2.5 (0.8)	2.3 (0.6)
Hyalinization	75.2 (161)	47 (9)	40 (4)	63 (22)	79 (11)	76 (47)	92 (68)
Lumen							
Open	8.4 (18)	0 (0)	0 (0)	3 (1)	22 (3)	18 (11)	4 (3)
Half-open	25.2 (54)	26 (5)	10 (1)	31 (11)	14 (2)	26 (16)	26 (19)
Absent	66.4 (142)	74 (14)	90 (9)	66 (23)	64 (9)	56 (35)	70 (52)

Data are % (n) unless stated otherwise.

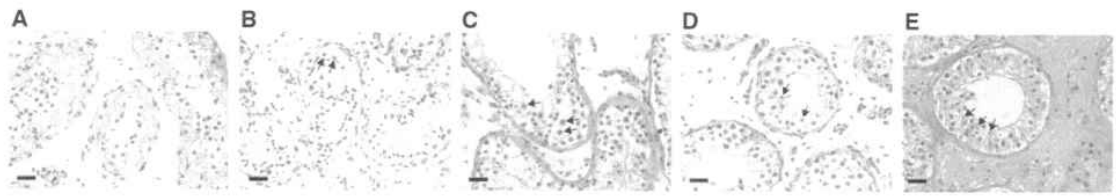

Figure 2. Orchiectomy specimens with their most advanced germ cell type. (**A**) No germ cells present. (**B**) Spermatogonia. (**C**) Spermatocytes. (**D**) Round spermatids. (**E**) Spermatozoa. Arrows indicate most advanced germ cells. Bar represents 20 μm.

women who initiated medical treatment in Tanner stage 4 or higher, complete spermatogenesis was observed in the orchiectomy specimen. For this group, it would theoretically be possible to perform TESE and cryopreserve the harvested spermatozoa from this specimen. Furthermore, the vast majority of transgender women still had immature germ cells in their orchiectomy specimen. This is the first study to report on people who initiated medical treatment in Tanner stage 2-3, and it was found that in 100% of their orchiectomy specimens immature germ cells were present. If maturation techniques like *in vitro* spermatogenesis become available in the future, cryopreservation of testicular tissue containing spermatogonial stem cells might be a promising option for this group to retain the possibility to have biological children. A complete absence of germ cells was only observed in transgender women who commenced GAHT as adult. Cessation of GAHT prior to gGAS did not affect the possibilities for fertility preservation, neither was there an effect of the duration of GAHT prior to gGAS.

Although some previous studies have been conducted on the influence of GAHT on spermatogenesis and testicular architecture, this is the first study taking age and pubertal stage at time of initiation of medical treatment into account. Between 1970 and 1990, several small studies were conducted reporting on 4–11 transgender women per study (Rodriguez-Rigau *et al.*, 1977; Lu and Steinberger, 1978; Payer *et al.*, 1979; Sapino *et al.*, 1987; Schulze, 1988; Venizelos and Paradinas, 1988). Therefore, no strong conclusions could be drawn, but results showed high proportions of tubular hyalinization and reduced spermatogenesis in all transgender women. The first large cohort study on this topic was performed in 2015 and assessed orchiectomy specimens of 108 transgender women from three clinics with different preoperative treatment protocols (6 weeks, 2 weeks or no discontinuation of GAHT prior to gGAS) (Schneider *et al.*, 2015). Their results on testicular histology and spermatogenic state were highly heterogeneous and did not show a relation with treatment strategy. Remarkably, a high number of transgender women (24% of

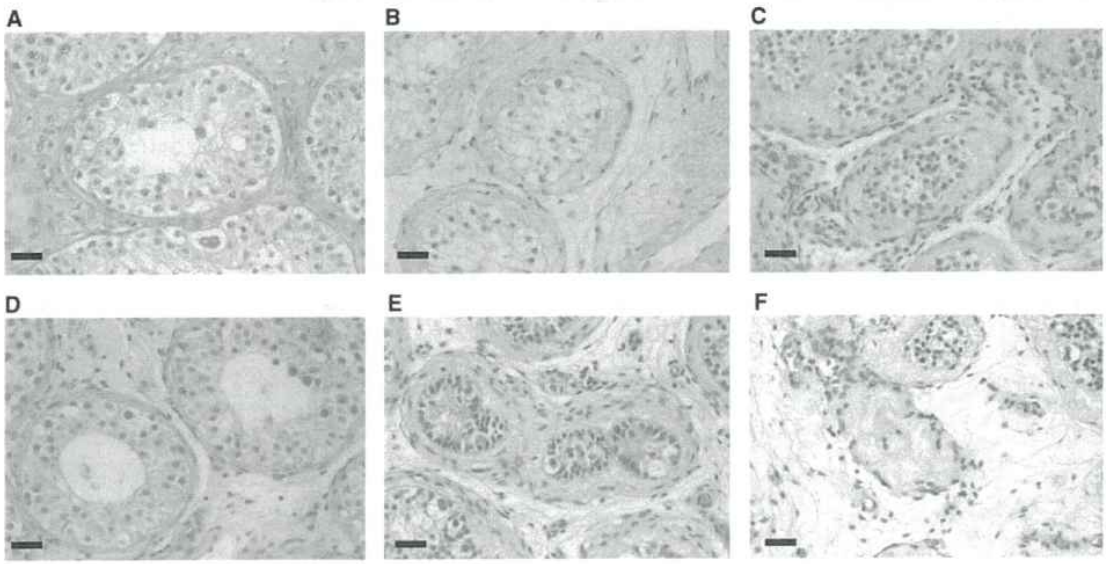

Figure 3. Different aspects of lumen and degrees of hyalinization of seminiferous tubules. (**A**) Open lumen. (**B**) Half-open lumen. (**C**) Absent lumen. (**D**) No hyalinization. (**E**) Mild hyalinization. (**F**) Severe hyalinization. Bar represents 20 μm.

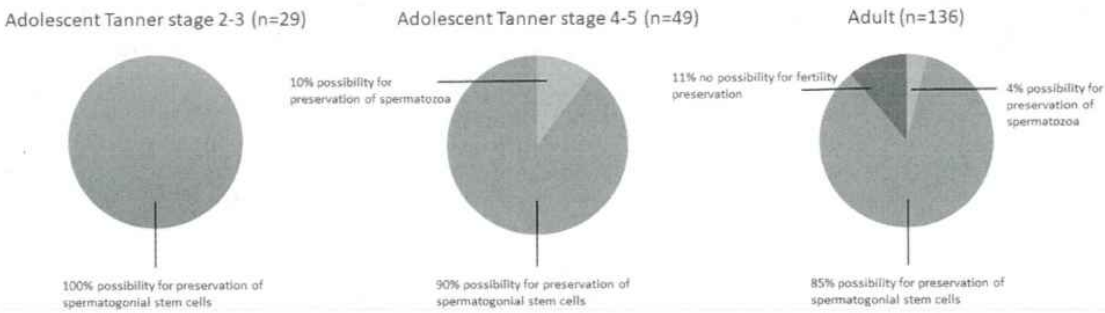

Figure 4. Comparison of the possibilities for fertility preservation between people who started medical treatment as adolescent in early puberty (Tanner stage 2-3) or late puberty (Tanner stage 4-5), and those who started as an adult (>18 years).

their study cohort) had complete spermatogenesis at time of gGAS. This finding was confirmed by Jiang *et al.* (2019) who even observed complete spermatogenesis in 40% of the 72 included transgender women. However, several other recent studies found lower percentages of complete spermatogenesis ranging from 0% to 11% of the study cohort (Jindarak *et al.*, 2018; Kent *et al.*, 2018; Matoso *et al.*, 2018; Vereecke *et al.*, 2021). It must be noted that hormonal and preoperative treatment protocols vary considerably within, and between, the different studies conducted on this topic. Therefore, for the current study, it was decided to only include transgender women who used estradiol in combination with testosterone suppressing therapy (triptorelin when initiated in adolescence, cyproterone acetate when initiated in adulthood), and to report results for those who continued GAHT until gGAS separate from those who discontinued four weeks prior to gGAS.

Since a study performed by Vereecke *et al.* (2021) also adhered strict in- and exclusion criteria that are similar to those in our adult subgroup, their results allow for the most accurate comparison. In addition, their method of analysis using immunohistochemistry to determine the most advanced germ cell type is similar to our study. In their

cohort of 97 transgender women, 12.4% had a complete absence of germ cells which is in line with the observed 11% in our cohort. However, none of their orchiectomy specimens showed complete spermatogenesis, as opposed to 4% of orchiectomy specimens in the adult subgroup of our cohort. Vereecke *et al.* (2021) also assessed the relationship between serum hormone levels and spermatogenic state in their cohort. They found that higher serum testosterone levels were associated with more advanced maturation, and higher serum estradiol levels were associated with a lower number of spermatogonia. However, the hormone levels were not measured on the day of gGAS, but at the last visit in the outpatient clinic 91.0 (57.5–152.5) days before surgery (Vereecke *et al.*, 2021). In contrast, Schneider *et al.* (2015) did collect serum and intratesticular testosterone levels on the day of gGAS but did not find an obvious correlation with spermatogenic state. In our gender identity clinic, hormone levels are not determined on the day of gGAS and laboratory results from the last visit in the outpatient clinic likely do not adequately reflect hormonal status during gGAS because of the preoperative cessation of GAHT 4 weeks prior to surgery. It was therefore decided not to assess this relationship in our cohort.

An interesting observation in the current study is that testicular histology and spermatogenesis seemed more negatively affected by GAHT in the adult subgroup compared to the adolescent subgroups, despite the lower mean duration of medical treatment in the former prior to gGAS. A higher percentage of hyalinization of the seminiferous tubules was observed in the adult subgroup, as well as a complete absence of germ cells in 15 orchiectomy specimens. The difference between the adult subgroup and the adolescent subgroups might be explained by age, lifestyle (a higher percentage of smokers and alcohol drinkers), higher dosages of estradiol or the use of cyproterone acetate instead of GnRHa as testosterone suppressing therapy. Whereas GnRHa only leads to inhibition of gonadotropin secretion, cyproterone acetate also has progestative effects and acts as a direct antagonist of the androgen receptor. It hereby inhibits the influence of androgens on the androgen-dependent organs, among which the testes. The latter might have more profound and irreversible effects on testicular tissue. Because of unwanted side-effects of cyproterone acetate (e.g. increased risk for meningioma), transgender women commencing GAHT in our clinic above the age of 18 years now receive GnRHa as testosterone suppressing therapy instead of cyproterone acetate. The potential consequence of irreversible infertility might be an extra reason to not prescribe cyproterone acetate anymore. In a future study, it would be interesting to assess if differences in testicular histology and spermatogenesis between adults and adolescents are still observed when they both receive GnRHa as testosterone suppressing therapy.

Cessation of GAHT prior to gGAS did not affect the possibilities for fertility preservation. In our study, the preoperative cessation of GAHT involved a period of four weeks, whereas the differentiation of spermatogonial stem cells into spermatozoa generally takes 10–12 weeks (Muciaccia *et al.*, 2013). Therefore, the period of cessation was most likely not long enough to influence the options for fertility preservation. If transgender women would be willing to discontinue GAHT for at least 12 weeks prior to gGAS, this might positively influence the chances of finding mature spermatozoa in the orchiectomy specimen. Moreover, they could even consider an attempt for cryopreservation of spermatozoa from a semen sample, obtained through ejaculation. However, it is unknown if spermatogenesis can recover if GAHT is stopped and how much time is needed for this purpose. Furthermore, it should not be underestimated that cessation of GAHT will result in increased testosterone levels which is likely to have negative physical and psychological consequences, and that masturbation is often not an option in transgender women due to severe genital dysphoria. A disadvantage of spermatozoa that are harvested from testicular tissue, is that they are not suitable for a minimally invasive and inexpensive IUI and can only be used for ICSI (Ombelet *et al.*, 2014). In addition, such ICSI treatments using surgically obtained spermatozoa are not always successful, since the cumulative ongoing pregnancy rate per cycle has been reported to be 22.8% and the live birth rate 22.3% (Meijerink *et al.*, 2016). Therefore, cryopreservation of a semen sample prior to initiation of GAHT remains the preferred method of fertility preservation in transgender women and harvesting germ cells from orchiectomy specimens might only be considered an alternative in those for whom this is not an option.

The lumina of the seminiferous tubules in those who initiated medical treatment in Tanner stage 2-3 were all either half-open, or absent. This observation might be explained by the immaturity of testicular tissue in early puberty, since an open lumen develops parallel to the development of spermatogenesis under the influence of increasing intratesticular testosterone levels. The fact that germ cells were encountered in all orchiectomy specimens from transgender women who initiated medical treatment as adolescent, is reassuring. Decision-making about fertility can be very difficult for adolescents since their intellectual, emotional and social immaturity may impede assessment and prediction of future desires regarding fertility and family planning. A recent study among transgender youth showed that 67% of young transgender women expressed a desire for future parenthood, but only 7% indicated to be frustrated if biological parenthood would not be feasible (Chiniara *et al.*, 2019). Another study, however, reported that 48% of transgender adolescents acknowledged that their desires regarding parenthood might change over time (Strang *et al.*, 2017). Reduced levels of gender dysphoria and improved mental health might result in an improved capability to establish romantic relationships and consider future family building. Our observation that immature germ cells remain present in testicular tissue during GAHT suggest that transgender adolescents still have potential options for fertility preservation after initiation of treatment by cryopreserving testicular tissue from orchiectomy specimen obtained during gGAS.

Cryopreservation of testicular tissue containing spermatogonial stem cells is mostly offered to pre-pubertal boys with cancer, prior to undergoing gonadotoxic therapies such as chemo- and radiotherapy, but some clinics also offer this option to transgender adolescents (Pang *et al.*, 2020). In the absence of complete spermatogenesis, the purpose of spermatogonial stem cell preservation in cisgender adolescents is to transplant these cells back into the testes years later, via injection into the rete testis space that is contiguous with all seminiferous tubules. Spermatogonial stem cells have the potential to colonize the testicular niche and regenerate spermatogenesis (David and Orwig, 2020). However, re-transplantation is not a feasible option for transgender women, as they will most likely use lifelong GAHT and many will undergo bilateral orchiectomy. Therefore, spermatogonial stem cell preservation will only be a viable method for fertility preservation in transgender women when other options for maturation become available, such as de novo testicular morphogenesis or *in vitro*

spermatogenesis. Although these techniques are successful in animal models, they are still experimental and far from the clinical realm (Pelzman *et al.*, 2020). Continuing research in this area will hopefully make these techniques available so that transgender adolescents, who are otherwise unable to have genetically related children, will be able to retain this possibility by cryopreserving testicular tissue containing spermatogonial stem cells. Furthermore, future research should focus on how GAHT influences the quality of germ cells and the safety of using cells harvested from orchiectomy specimens, for reproductive techniques. Lastly, it is important to examine how transgender women feel about fertility preservation options in orchiectomy specimens obtained during gGAS.

A limitation of this study is the lack of data on serum hormone levels on the day of gGAS. We were therefore unable to verify if the transgender women who were asked to temporarily stop hormonal treatment four weeks prior to surgery actually did so, and if people with complete spermatogenesis were compliant to treatment. However, the last known serum testosterone levels before gGAS were suppressed in all participants. Furthermore, despite our efforts to create a homogeneous study population, by excluding people who used estrogen monotherapy and those who used spironolactone as anti-androgenic treatment, participants still used varying formulations of estrogens and switched between different formulations over time. We were therefore unable to assess if different estrogen formulations have different effects on testicular histology and spermatogenesis. Strengths of our study include the large sample size of 214 transgender women, and the creation of six subgroups to allow for comparison between different preoperative protocols before gGAS and pubertal stage at initiation of medical treatment. Hereby, this study provides novel information about the influence of starting medical treatment in early puberty on testicular function, and its consequences for the possibilities for fertility preservation at time of gGAS. This is relevant because we are seeing a global increase of the number of referrals of adolescents to gender identity clinics (Handler *et al.*, 2019; Kaltiala *et al.*, 2020). At the same time, there is increasing controversy over the provision of GAHT to adolescents, with the negative effect on fertility often cited as an argument for limiting adolescents' access to gender-affirming care (The Economist, 2020). Our observation that the spermatogonial stem cell pool is still intact in people who initiated GAHT during adolescence is therefore valuable information in this debate.

Conclusion

Counseling of transgender women about the effect of medical treatment on fertility and the currently available options for fertility preservation remains essential. However, for some transgender women with a wish for fertility preservation, there are barriers that prevent the use of semen cryopreservation. For example, some initiate medical treatment in early puberty before the development of complete spermatogenesis, some are unable to masturbate, and some feel that a temporary cessation of GAHT would be too psychologically and physically disruptive. The results of this study show that there may still be options for fertility preservation using orchiectomy specimens obtained during gGAS. In a small percentage of transgender women who initiated medical treatment in Tanner stage 4 or higher, spermatozoa could have been harvested from the orchiectomy specimen at time of gGAS. In addition, the vast majority (>85%) of transgender women in our cohort could still opt for cryopreservation of testicular tissue harboring spermatogonial stem cells. A complete absence of germ cells was only observed in a small number (7%) of transgender women in our cohort, who all commenced GAHT as adult. The possibilities for fertility preservation seem irrespective of preoperative cessation of GAHT and the duration of GAHT prior to gGAS.

Initiation of medical treatment in early pubertal adolescents (Tanner stage 2-3) limits the ability to retrieve mature spermatozoa that can directly be used for assisted reproductive techniques. However, if maturation techniques like *in vitro* spermatogenesis become available in the future, harvesting germ cells from orchiectomy specimens might be a promising option for those who are otherwise unable to have biological children.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

Part of the data underlying this article are available in the article and in its online supplementary material, the rest of the data will be shared on reasonable request to the corresponding author.

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Authors' roles

I.d.N.—conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript. C.L.M.—conception and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for intellectual content. A.M.—analysis and interpretation of data, critical revision of the manuscript for intellectual content. Y.S.—acquisition of data, analysis and interpretation of data, drafting of manuscript. E.M.H.—acquisition of data, drafting of manuscript. W.B.v.d.S.—acquisition of data, critical revision of the manuscript for intellectual content. S.E.H.—analysis and interpretation of data, critical revision of the manuscript for intellectual content. M.d.H.—conception and design, analysis and interpretation of data, critical revision of the manuscript for intellectual content. J.H.—conception and design, analysis and interpretation of data, critical revision of the manuscript for intellectual content. A.M.M.v.P.—conception and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for intellectual content. N.M.v.M.—conception and design, analysis and interpretation of data, critical revision of the manuscript for intellectual content. All authors approved the final version of the manuscript.

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Conflict of interest

None.

References

Adeleye AJ, Reid G, Kao CN, Mok-Lin E, Smith JF. Semen parameters among transgender women with a history of hormonal treatment. *Urology* 2019;**124**:136–141.

APA. *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. Arlington, VA: American Psychiatric Association, 2013.

Auer MK, Fuss J, Nieder TO, Briken P, Biedermann SV, Stalla GK, Beckmann MW, Hildebrandt T. Desire to have children among transgender people in Germany: a cross-sectional multi-center study. *J Sex Med* 2018;**15**:757–767.

Brik T, Vrouenraets L, Schagen SEE, Meissner A, de Vries MC, Hannema SE. Use of fertility preservation among a cohort of transgirls in the Netherlands. *J Adolesc Health* 2019;**64**:589–593.

Chen D, Matson M, Macapagal K, Johnson EK, Rosoklija I, Finlayson C, Fisher CB, Mustanski B. Attitudes toward fertility and reproductive health among transgender and gender-nonconforming adolescents. *J Adolesc Health* 2018;**63**:62–68.

Chiniara LN, Viner C, Palmert M, Bonifacio H. Perspectives on fertility preservation and parenthood among transgender youth and their parents. *Arch Dis Child* 2019;**104**:739–744.

David S, Orwig KE. Spermatogonial stem cell culture in oncofertility. *Urol Clin North Am* 2020;**47**:227–244.

Handler T, Hojilla JC, Varghese R, Wellenstein W, Satre DD, Zaritsky E. Trends in referrals to a pediatric transgender clinic. *Pediatrics* 2019;**144**:e20191368.

Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V, T'Sjoen GG. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017;**102**:3869–3903.

Jiang DD, Swenson E, Mason M, Turner KR, Dugi DD, Hedges JC, Hecht SL. Effects of estrogen on spermatogenesis in transgender women. *Urology* 2019;**132**:117–122.

Jindarak S, Nilprapha K, Atikankul T, Angspatt A, Pungrasmi P, Iamphongsai S, Promniyom P, Suwajo P, Selvaggi G, Tiewtranon P. Spermatogenesis abnormalities following hormonal therapy in transwomen. *Biomed Res Int* 2018;**2018**:7919481.

Johnsen SG. Testicular biopsy score count—a method for registration of spermatogenesis in human testes: normal values and results in 335 hypogonadal males. *Hormones* 1970;**1**:2–25.

Kaltiala R, Bergman H, Carmichael P, de Graaf NM, Rischel KE, Frisen L, Schorkopf M, Suomalainen L, Waehre A. Time trends in referrals to child and adolescent gender identity services: a study in four Nordic countries and in the UK. *Nord J Psychiatry* 2020;**74**:40–44.

Kent MA, Winoker JS, Grotas AB. Effects of feminizing hormones on sperm production and malignant changes: microscopic examination of post orchiectomy specimens in transwomen. *Urology* 2018;**121**:93–96.

Lu CC, Steinberger A. Effects of estrogen on human seminiferous tubules: light and electron microscopic analysis. *Am J Anat* 1978;**153**:1–13.

Matoso A, Khandakar B, Yuan S, Wu T, Wang LJ, Lombardo KA, Mangray S, Mannan A, Yakirevich E. Spectrum of findings in orchiectomy specimens of persons undergoing gender confirmation surgery. *Hum Pathol* 2018;**76**:91–99.

Meijerink AM, Cissen M, Mochtar MH, Fleischer K, Thoonen I, de Melker AA, Meissner A, Repping S, Braat DD, van Wely M *et al.* Prediction model for live birth in ICSI using testicular extracted sperm. *Hum Reprod* 2016;**31**:1942–1951.

Muciaccia B, Boitani C, Berloco BP, Nudo F, Spadetta G, Stefanini M, de Rooij DG, Vicini E. Novel stage classification of human spermatogenesis based on acrosome development. *Biol Reprod* 2013;**89**:60.

Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* 1998;**17**:857–872.

Ombelet W, Dhont N, Thijssen A, Bosmans E, Kruger T. Semen quality and prediction of IUI success in male subfertility: a systematic review. *Reprod Biomed Online* 2014;**28**:300–309.

Pang KC, Peri AJS, Chung HE, Telfer M, Elder CV, Grover S, Jayasinghe Y. Rates of fertility preservation use among transgender adolescents. *JAMA Pediatr* 2020;**174**:890.

Payer AF, Meyer WJ 3rd, Walker PA. The ultrastructural response of human Leydig cells to exogenous estrogens. *Andrologia* 1979;**11**:423–436.

Pelzman DL, Orwig KE, Hwang K. Progress in translational reproductive science: testicular tissue transplantation and *in vitro* spermatogenesis. *Fertil Steril* 2020;**113**:500–509.

Rodriguez-Rigau LJ, Tcholakian RK, Smith KD, Steinberger E. *In vitro* steroid metabolic studies in human testes I: effects of estrogen on progesterone metabolism. *Steroids* 1977;**29**:771–786.

Sapino A, Pagani A, Godano A, Bussolati G. Effects of estrogens on the testis of transsexuals: a pathological and immunocytochemical study. *Virchows Arch A Pathol Anat Histopathol* 1987;**411**:409–414.

Sato T, Katagiri K, Gohbara A, Inoue K, Ogonuki N, Ogura A, Kubota Y, Ogawa T. *In vitro* production of functional sperm in cultured neonatal mouse testes. *Nature* 2011;**471**:504–507.

Schneider F, Kliesch S, Schlatt S, Neuhaus N. Andrology of male-to-female transsexuals: influence of cross-sex hormone therapy on testicular function. *Andrology* 2017;**5**:873–880.

Schneider F, Neuhaus N, Wistuba J, Zitzmann M, Heß J, Mahler D, van Ahlen H, Schlatt S, Kliesch S. Testicular functions and clinical characterization of patients with gender dysphoria (GD) undergoing sex reassignment surgery (SRS). *J Sex Med* 2015;**12**:2190–2200.

Schulze C. Response of the human testis to long-term estrogen treatment: morphology of Sertoli cells, Leydig cells and spermatogonial stem cells. *Cell Tissue Res* 1988;**251**:31–43.

Strang JF, Jarin J, Call D, Clark B, Wallace GL, Anthony LG, Kenworthy L, Gomez-Lobo V. Transgender youth fertility attitudes questionnaire: measure development in nonautistic and autistic transgender youth and their parents. *J Adolesc Health* 2018;**62**:128–135.

The Economist. 2020. A new push to ban medical treatments for transgender children. *The Economist*. Washinton, DC.

van der Sluis WB, de Nie I, Steensma TD, van Mello NM, Lissenberg-Witte BI, Bouman MB. Surgical and demographic trends in genital gender-affirming surgery in transgender women: 40 years of experience in Amsterdam. *Br J Surg* 2021;doi: 10.1093/bjs/znab213.

Venizelos ID, Paradinas FJ. Testicular atrophy after oestrogen therapy. *Histopathology* 1988;**12**:451–454.

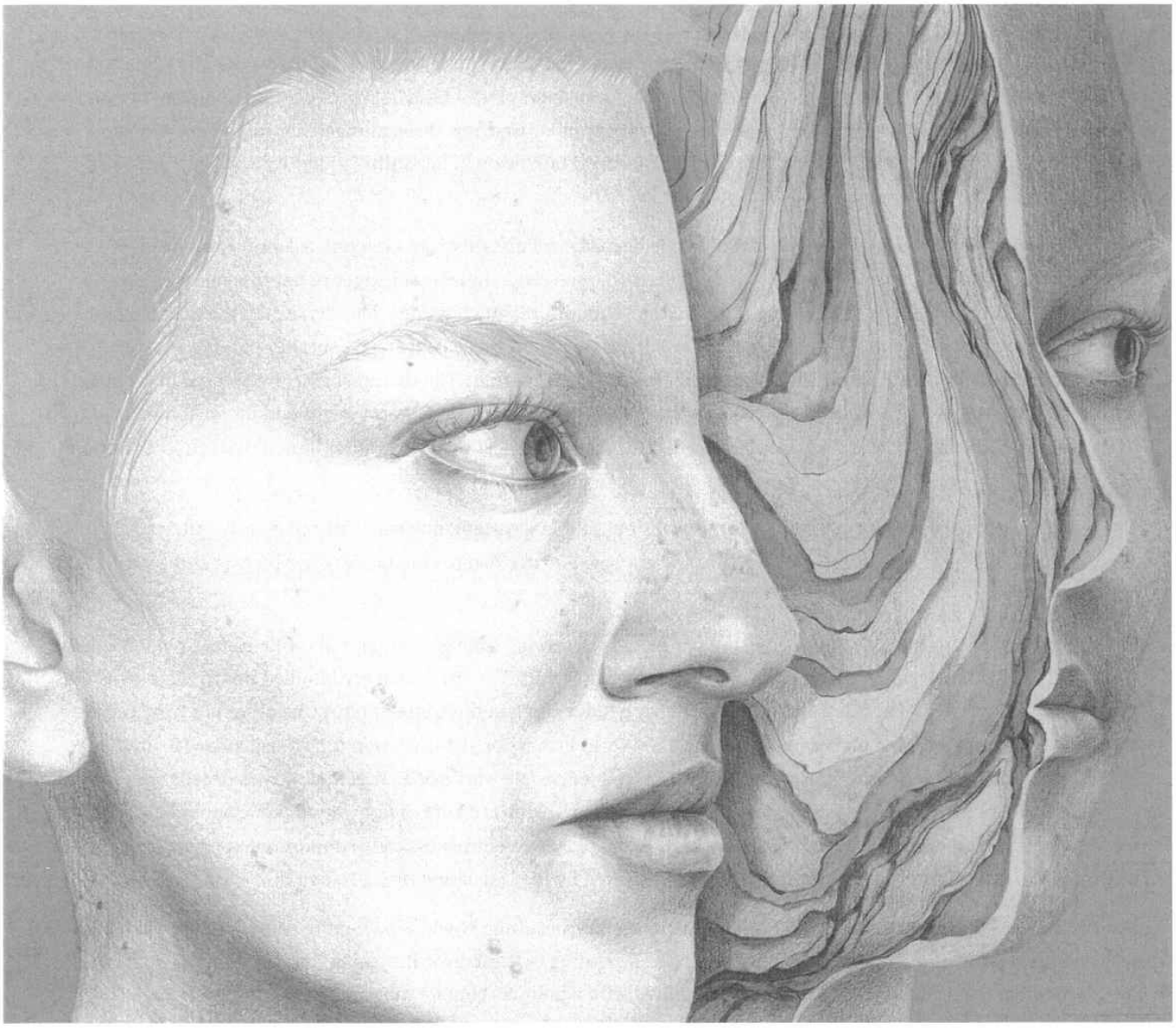
Vereecke G, Defreyne J, Van Saen D, Collet S, Van Dorpe J, T'Sjoen G, Goossens E. Characterisation of testicular function and spermatogenesis in transgender women. *Human Reproduction* 2021;**36**:5–15.

Vyas N, Douglas CR, Mann C, Weimer AK, Quinn MM. Access, barriers, and decisional regret in pursuit of fertility preservation among transgender and gender-diverse individuals. *Fertil Steril* 2020: 1029–1034.

Wallace SA, Blough KL, Kondapalli LA. Fertility preservation in the transgender patient: expanding oncofertility care beyond cancer. *Gynecol Endocrinol* 2014;**30**:868–871.

The mental health establishment is failing trans kids

Gender-exploratory therapy is a key step. Why aren't therapists providing it?



Daryn Ray for The Washington Post

By Laura Edwards-Leeper and Erica Anderson

November 24, 2021 at 5:54 p.m. EST

CORRECTION

A previous version of this essay said that a quarter of study subjects who reversed their gender transitions did not report this change to their doctors. In fact, three-quarters did not share the information.

At 13, Patricia told her parents she was a transgender boy. She had never experienced any gender dysphoria — distress at a disconnect between gender identity and the sex assigned at birth — she said. But a year earlier, she'd been sexually assaulted by an older girl. Soon after this trauma, she met another older girl who used they/them pronouns and introduced her to drugs, violent pornography and the notion of dissociation from her body. Her lingering psychic wounds, coinciding with a raft of new and unsettling ideas, plunged her into depression and anxiety. Patricia's parents took her to a therapist so she could talk through her shifting identity and acute mood swings.

The job of a mental health provider here should have been clear: Perform an assessment, ask how long she'd experienced dysphoria and investigate how mental health issues and any other changes in her life might be contributing to it. Instead, on first meeting, the therapist simply affirmed her new identity, a step that can lead to hormonal and eventually surgical treatments. Was Patricia ready for these next steps — or, her parents wondered, was this a normal bout of teenage confusion stemming from a recent trauma? The therapist instructed them to "support" their child's trans self-diagnosis and to socially transition her. If they didn't, Patricia might end her own life: 41 percent of unsupported children commit suicide, they were told. Would Patricia's parents rather have a dead child or a trans one?

They sought another therapist, one who was more curious and less certain, one who listened closely. After a year of exploring who she was, Patricia no longer felt she was a boy. She decided to stop binding her breasts and wearing boys' clothes.

We are both psychologists who have dedicated our careers to serving transgender patients with ethical, evidence-based treatment. But we see a surge of gender dysphoria cases like Patricia's — cases that are handled poorly. One of us was the founding psychologist in 2007 of the first pediatric gender clinic in the United States; the other is a transgender woman. We've held recent leadership positions in the World Professional Association for Transgender Health (WPATH), which writes the standards of care for transgender people worldwide. Together, across decades of doing this work, we've helped hundreds of people transition their genders. This is an era of ugly moral panic about bathrooms, woke indoctrination and identity politics in general. In response, we enthusiastically support the appropriate gender-affirming medical care for trans youth, and we are disgusted by the legislation trying to ban it.

But the number of adolescents requesting medical care is skyrocketing: Now 1.8 percent of people under 18 identify as transgender, double the figure from five years earlier, according to the Trevor Project. A flood of referrals to mental health providers and gender medical clinics, combined with a political climate that sees the treatment of each individual patient as a litmus test of social tolerance, is spurring many providers into sloppy, dangerous care. Often from a place of genuine concern, they are hastily dispensing medicine or recommending medical doctors prescribe it — without following the strict guidelines that govern this treatment. Canada, too, is following our lead: A study of 10 pediatric gender clinics there found that half do not require psychological assessment before initiating puberty blockers or hormones.

The standards of care recommend mental health support and comprehensive assessment for all dysphoric youth before starting medical interventions. The process, done conscientiously, can take a few months (when a young person's gender has been persistent and there are no simultaneous mental health issues) or up to several years in complicated cases. But few are trained to do it properly, and some clinicians don't even believe in it, contending without evidence that treating dysphoria medically will resolve other mental health issues. Providers and their behavior haven't been closely studied, but we find evidence every single day, from our peers across the country and concerned parents who reach out, that the field has moved from a more nuanced, individualized and developmentally appropriate assessment process to one where every problem looks like a medical one that can be solved quickly with medication or, ultimately, surgery. As a result, we may be harming some of the young people we strive to support — people who may not be prepared for the gender transitions they are being rushed into.

American opinions about transgender youth have shifted dramatically in the past 15 years. The pendulum has swung from a vile fear and skepticism around ever treating adolescents medically to what must be described, in some quarters, as an overcorrection. Now the treatment pushed by activists, recommended by some providers and taught in many training workshops is to affirm without question. "We don't actually have data on whether psychological assessments lower regret rates," Johanna Olson-Kennedy, a pediatrician at Children's Hospital in Los Angeles who is skeptical of therapy requirements and gives hormones to children as young as 12 (despite a lack of science supporting this practice, as well), told the Atlantic. "I don't send someone to a therapist when I'm going to start them on insulin." This perspective writes off questions about behavioral and mental health, seeing them as a delaying tactic or a dodge, a way of depriving desperate people of the urgent care they clearly need.

But comprehensive assessment and gender-exploratory therapy is the most critical part of the transition process. It helps a young person peel back the layers of their developing adolescent identity and examine the factors that contribute to their dysphoria. In this stage, patients reflect on the duration of the dysphoria they feel; the continuum of gender; the intersection with sexual orientation; what medical interventions might realistically entail; social media, Internet and peer influences; how other factors (e.g., autism, trauma, eating disorders/body image concerns, self-esteem, depression, anxiety) may help drive dysphoria, rather than assuming that they are always a result of dysphoria; family dynamics and social/peer relationships; and school/academic challenges. The messages that teens get from TikTok and other sources may not be very productive for understanding this constellation of issues.

There are several reasons the process can move too quickly and hurtle toward medical treatment. For one, the stigma around mental health in general, along with the trauma caused to transgender adults by the health-care field in the past (yes, including conversion therapy), has made our peers extremely skeptical of becoming "gatekeepers" — experts who deny the needed help because they supposedly know best. Slowing down the process and encouraging deeper, thoughtful exploration is considered, many tell us, unnecessary and unaffirming. Providers may also be afraid of being cast as transphobic bigots by their local colleagues and referral sources if they engage in gender exploring therapy with patients, as some have equated this with conversion therapy. We've personally experienced this backlash at professional conferences.

All this means only that the purpose of assessment is improperly understood. The approach WPATH recommends is collaborative and aims to provide a developmentally appropriate process that involves the parents and takes the complexities of adolescence into consideration. (The constituency of agitated parents who feel excluded is also growing rapidly. These are not conservative evangelicals who don't believe trans people exist or deserve treatment. They're usually progressive, educated, loving people who all say, *If our kid is really trans, we'll fully support them. We just want to be as sure as possible, and we can't find a provider who will actually engage in gender exploring therapy. Instead, doctors and psychologists and social workers are ready to start hormones after one short visit.*)

Another reason that teens can receive substandard mental health care is that gender clinics are disastrously overwhelmed. Most have a single social worker who completes a brief "intake," relying instead on other mental health clinicians in the community to assess patients and offer their conclusions. Frequently, those community clinicians, just like the parents, assume that a more comprehensive assessment will occur in the gender specialty clinic. But in our experience, and based on what our colleagues share, this is rarely the case. Most clinics appear to assume that a referral means a mental health provider in the community has diagnosed gender dysphoria and thereby given the green light for medical intervention.

When working in gender clinics, we've also both received letters from therapists who had "assessed" patients they were referring to us. An astonishing number of these were nothing but a paragraph that stated the youth identified as trans, had dysphoria and wanted hormones, so that course was recommended. There are nearly 200,000 members of the American Psychological Association and the American Psychiatric Association. Add to that the clinical social workers, marriage counselors and family therapists. The overwhelming majority of those well-intentioned professionals receive limited or no training in the assessment of gender-diverse youth. (We receive requests frequently from people eager for more comprehensive, nuanced trainings, which we both deliver.) In simple terms, the demand for competent care has outstripped the supply of competent providers.

In professional circles, we hear from pediatric endocrinologists and others who prescribe hormones for trans youth. Many openly discuss how they use the adult informed-consent model of care with their teen patients, which almost always means no mental health involvement and sometimes no parent input, either. "If you are trans, I believe you," says A.J. Eckert, the medical director of Anchor Health Initiative in Connecticut. Eckert is wary of psychologists who follow the guidelines by completing a comprehensive assessment before recommending medical intervention for youths. "Gender-affirming medicine," Eckert holds, means that "you are best equipped to make decisions about your own body," full stop. These providers do not always realize they've confessed to ignoring the standards of care. (Contacted by The Post for comment on this essay, Eckert said that "no medical or surgical interventions are provided to anyone who has not started puberty" but added that, as Anchor Health sees it, "Therapy is not a requirement in this approach because being trans is not a pathology.")

Some providers may move quickly because they believe that an adolescent's clarity around their gender identity is no different than that of transgender adults, whose care is now typically based on simple informed consent. Some assume that a person with gender dysphoria who declares they are transgender is transgender and needs medical interventions immediately. Yet we know this is not always true. In a recent study of 100 detransitioners, for instance, 38 percent reported that they believed their original dysphoria had been caused by "something specific, such as trauma, abuse, or a mental health condition." Fifty-five percent said they "did not receive an adequate evaluation from a doctor or mental health professional before starting transition."

A handful of studies supposedly showing the suicide risk of gender minority youth who are not supported are also not entirely conclusive. The term "support," for instance, is defined differently across studies, and it is never defined as "starting medical interventions." Supporting trans youth may include using the correct name/pronouns or allowing the young person to present in a way that aligns with their affirmed gender (e.g., clothing, hairstyle). These studies also show correlations between teen-transition hurdles and suicidality, but not causal relationships. Suicide is a horrifying outcome for too many gender-diverse youth, but its specter should not be used to push forward unrelated medical treatment without professional care or attention for each patient.

Longer-term longitudinal studies are needed to better understand the role of medical interventions on lifetime psychological health, particularly with the newer subset of adolescents presenting with no childhood dysphoria and significant mental health concerns. Research is needed to help determine whether quick medical treatment or a more cautious approach is best in these cases. Based on our experience with patients, we suspect that there will be variability based on age, when gender identity questions first emerged and other factors — which is why an individualized approach with careful assessment is so critical.

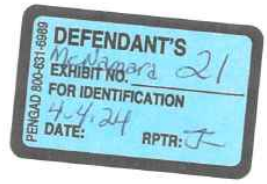
Trans youth, more than most patients in the health-care system, require an interdisciplinary approach: Their doctors rely on mental health colleagues for direction, and it is crucial that those therapists take the reins. Without proper assessment, many youths are being rushed toward the medical model, and we don't know if they will be liberated or restrained by it. National figures do not yet exist, but the rising number of detransitioners that clinicians report seeing (they are forming support groups online) indicates that this approach can backfire. This is not the most common outcome of a transition process, but it is hardly unheard of, either. These are typically youth who experienced gender dysphoria and other complex mental health issues, rushed to medicalize their bodies and regretted it later. Only a quarter of them told their doctors they had reversed their transitions, making this population especially hard to track.

Many trans activists want to silence detransitioners or deny their existence, because those cases do add fuel to the conservative agenda that is pushing to deny medical treatment to all transgender young people. (Those conservative views are unacceptable, and medically unsound.) Instead, we should be learning from them and returning to the empirically supported careful assessment model recommended by WPATH. And none of this means that we shouldn't be listening to the views of gender-diverse teens; it only means that we should listen in the fullest and most probing way possible.

The pressure by activist medical and mental health providers, along with some national LGBT organizations to silence the voices of detransitioners and sabotage the discussion around what is occurring in the field is unconscionable. Not only is it harmful to detransitioned young people — to be made to feel as if their lived experiences are not valid, the very idea that the gender-transition treatment is meant to remedy — but it will undoubtedly raise questions regarding the objectivity of our field and our commitment to help trans people. The fact that some people detransition does not mean that transgender people should not receive the services they need.

The energy currently spent fighting this political battle would be much better directed toward improving care for all gender-diverse young people. They deserve nothing less.

Intended for healthcare professionals



Feature BMJ Investigation

Gender dysphoria in young people is rising—and so is professional disagreement

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More children and adolescents are identifying as transgender and are being offered medical treatment, especially in the US—but some providers and European authorities are urging caution because of a lack of strong evidence. **Jennifer Block** reports

Last October the American Academy of Pediatrics (AAP) gathered inside the Anaheim Convention Center in California for its annual conference. Outside, several dozen people rallied to hear speakers including Abigail Martinez, a mother whose child began hormone treatment at age 16 and died by suicide at age 19. Supporters chanted the teen's given name, Yaeli; counter protesters chanted, "Protect trans youth!" For viewers on a livestream, the feed was interrupted as the two groups fought for the camera.

The AAP conference is one of many flashpoints in the contentious debate in the United States over if, when, and how children and adolescents with gender dysphoria should be medically or surgically treated. US medical professional groups are aligned in support of "gender affirming care" for gender dysphoria, which may include gonadotrophin releasing hormone analogues (GnRHa) to suppress puberty; oestrogen or testosterone to promote secondary sex characteristics; and surgical removal or augmentation of breasts, genitals, or other physical features. At the same time, however, several European countries have issued guidance to limit medical intervention in minors, prioritising psychological care.

The discourse is polarised in the US. Conservative politicians, pundits, and social media influencers accuse providers of pushing "gender ideology" and even "child abuse," lobbying for laws banning medical transition for minors. Progressives argue that denying access to care is a transphobic violation of human rights. There's little dispute within the medical community that children in distress need care, but concerns about the rapid widespread adoption of interventions and calls for rigorous scientific review are coming from across the ideological spectrum.1

The surge in treatment of minors

More adolescents with no history of gender dysphoria—predominantly birth registered females2—are presenting at r clinics. A recent analysis of insurance claims by Komodo Health found that nearly 18 000 US minors began puberty blockers or hormones from 2017 to 2021, the number rising each year.34 Surveys aiming to measure

prevalence have found that about 2% of high school aged teens identify as "transgender."**5** These young people are also more likely than their cisgender peers to have concurrent mental health and neurodiverse conditions including depression, anxiety, attention deficit disorders, and autism.**6** In the US, although Medicaid coverage varies by state and by treatment, the Biden administration has warned states that not covering care is in violation of federal law prohibiting discrimination.**7** Meanwhile, the number of private clinics that focus on providing hormones and surgeries has grown from just a few a decade ago to more than 100 today.**4**

As the number of young people receiving medical transition treatments rises, so have the voices of those who call themselves "detransitioners" or "retransitioners," some of whom claim that early treatment caused preventable harm.**8** Large scale, long term research is lacking,**9** and researchers disagree about how to measure the phenomenon, but two recent studies suggest that as many as 20-30% of patients may discontinue hormone treatment within a few years.**1011** The World Professional Association for Transgender Health (WPATH) asserts that detransition is "rare."**12**

Chloe Cole, now aged 18, had a double mastectomy at age 15 and spoke at the AAP rally. "Many of us were young teenagers when we decided, on the direction of medical experts, to pursue irreversible hormone treatments and surgeries," she read from her tablet at the rally, which had by this time moved indoors to avoid confrontation. "This is not informed consent but a decision forced under extreme duress."

Scott Hadland, chief of adolescent medicine at Massachusetts General Hospital and Harvard Medical School, dismissed the "handful of cruel protesters" outside the AAP meeting in a tweet that morning. He wrote, "Inside 10 000 pediatricians stand in solidarity for trans & gender diverse kids & their families to receive evidence-based, lifesaving, individualized care."**13**

Same evidence, divergent recommendations

Three organisations have had a major role in shaping the US's approach to gender dysphoria care: WPATH, the AAP, and the Endocrine Society (see box). On 15 September 2022 WPATH published the eighth edition of its Standards of Care for the Health of Transgender and Gender Diverse People, with new chapters on children and adolescents and no minimum age requirements for hormonal and surgical treatments.**212** GnRHa treatment, says WPATH, can be initiated to arrest puberty at its earliest stage, known as Tanner stage 2.

The Endocrine Society also supports hormonal and surgical intervention in adolescents who meet criteria in clinical practice guidelines published in 2009 and updated in 2017.**14** And the AAP's 2018 policy statement, *Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents*, says that "various interventions may be considered to better align" a young person's "gender expression with their underlying identity."**15** Among the components of "gender affirmation" the AAP names social transition, puberty blockers, sex hormones, and surgeries. Other prominent professional organisations, such as the American Medical Association, have issued policy statements in opposition to legislation that would curtail access to medical treatment for minors.**16171819**

These documents are often cited to suggest that medical treatment is both uncontroversial and backed by rigorous science. "All of those medical societies find such care to be evidence-based and medically necessary," stated a recent article on transgender healthcare for children published in *Scientific American*.**20** "Transition related healthcare is not controversial in the medical field," wrote Gillian Branstetter, a frequent spokesperson on transgender issues currently with the American Civil Liberties Union, in a 2019 guide for reporters.**21** Two physicians [illegible] attorney from Yale recently opined in the *Los Angeles Times* that "gender-affirming care is standard medical [illegible]supported by major medical organizations . . . Years of study and scientific scrutiny have established safe,

evidence-based guidelines for delivery of lifesaving, gender-affirming care."**22** Rachel Levine, the US assistant secretary for health, told National Public Radio last year regarding such treatment, "There is no argument among medical professionals."**23**

Internationally, however, governing bodies have come to different conclusions regarding the safety and efficacy of medically treating gender dysphoria. Sweden's National Board of Health and Welfare, which sets guidelines for care, determined last year that the risks of puberty blockers and treatment with hormones "currently outweigh the possible benefits" for minors.**24** Finland's Council for Choices in Health Care, a monitoring agency for the country's public health services, issued similar guidelines, calling for psychosocial support as the first line treatment.**25** (Both countries restrict surgery to adults.)

Medical societies in France, Australia, and New Zealand have also leant away from early medicalisation.**2627** And NHS England, which is in the midst of an independent review of gender identity services, recently said that there was "scarce and inconclusive evidence to support clinical decision making"**28** for minors with gender dysphoria**29** and that for most who present before puberty it will be a "transient phase," requiring clinicians to focus on psychological support and to be "mindful" even of the risks of social transition.**30**

Box **The origins of paediatric gender medicine in the United States**

The World Professional Association for Transgender Health (WPATH) began as a US based advocacy group and issued the first edition of the Standards of Care in 1979, when it was serving a small population of mostly adult male-to-female transsexuals. "WPATH became the standard because there was nobody else doing it," says Erica Anderson, a California based clinical psychologist and former WPATH board member. The professional US organisations that lined up in support "looked heavily to WPATH and the Endocrine Society for their guidance," she told *The BMJ*.

The Endocrine Society's guidance for adolescents grew out of clinicians' research in the Netherlands in the late 1990s and early 2000s. Peggy Cohen-Kettenis, a Utrecht gender clinic psychologist, collaborated with endocrinologists in Amsterdam, one of whom had experience of prescribing gonadotrophin releasing hormone analogues, relatively new at the time. Back then, gender dysphoric teens had to wait until the age of majority for sex hormones, but the team proposed that earlier intervention could benefit carefully selected minors.**40**

The clinic treated one natal female patient with triptorelin, published a case study and feasibility proposal, and began treating a small number of children at the turn of the millennium. The Dutch Protocol was published in 2006, referring to 54 children whose puberty was being suppressed and reporting preliminary results on the first 21.**41** The researchers received funding from Ferring Pharmaceuticals, the manufacturer of triptorelin.

In 2007 the endocrinologist Norman Spack began using the protocol at Boston Children's Hospital and joined Cohen-Kettenis and her Dutch colleagues in writing the Endocrine Society's first clinical practice guideline.**42** When that was published in 2009, puberty had been suppressed in just over 100 gender dysphoric young people.**40**

American Academy of Pediatrics (AAP) committee members began discussing the need for a statement in 2014, four years before publication, says Jason Rafferty, assistant professor of paediatrics and psychiatry at Brown University, Rhode Island, and the statement's lead author. "The AAP recognised that it had a responsibility to provide some clinical guidance, but more importantly to come out with a statement that said we need research, we need to integrate the principles of gender affirmative care into medical education and into ı health," he says. "What our policy statement is not meant to be is a protocol or guidelines in and of nselves."

"Don't call them evidence based"

"The brief history of guidelines is that, going back more than 30 years ago, experts would write articles and so on about what people should do. But formal guidelines as we think of them now were seldom or non-existent," says Gordon Guyatt, distinguished professor in the Department of Health Research Methods, Evidence, and Impact at McMaster University, Ontario.

That led to the movement towards developing criteria for what makes a "trustworthy guideline," of which Guyatt was a part.**31** One pillar of this, he told *The BMJ*, is that they "are based on systematic review of the relevant evidence," for which there are also now standards, as opposed to a traditional narrative literature review in which "a bunch of experts write whatever they felt like using no particular standards and no particular structure."

Mark Helfand, professor of medical informatics and clinical epidemiology at Oregon Health and Science University, says, "An evidence based recommendation requires two steps." First, "an unbiased, thorough, critical systematic review of all the relevant evidence." Second, "some commitment to link the strength of the recommendations to the quality of the evidence."

The Endocrine Society commissioned two systematic reviews for its clinical practice guideline, *Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons*: one on the effects of sex steroids on lipids and cardiovascular outcomes, the other on their effects on bone health.**3233** To indicate the quality of evidence underpinning its various guidelines, the Endocrine Society employed the GRADE system (grading of recommendations assessment, development, and evaluation) and judged the quality of evidence for all recommendations on adolescents as "low" or "very low."

Guyatt, who co-developed GRADE, found "serious problems" with the Endocrine Society guidelines, noting that the systematic reviews didn't look at the effect of the interventions on gender dysphoria itself, arguably "the most important outcome." He also noted that the Endocrine Society had at times paired strong recommendations—phrased as "we recommend"—with weak evidence. In the adolescent section, the weaker phrasing "we suggest" is used for pubertal hormone suppression when children "first exhibit physical changes of puberty"; however, the stronger phrasing is used to "recommend" GnRHa treatment.

"GRADE discourages strong recommendations with low or very low quality evidence except under very specific circumstances," Guyatt told *The BMJ*. Those exceptions are "very few and far between," and when used in guidance, their rationale should be made explicit, Guyatt said. In an emailed response, the Endocrine Society referenced the GRADE system's five exceptions, but did not specify which it was applying.

Helfand examined the recently updated WPATH Standards of Care and noted that it "incorporated elements of an evidence based guideline." For one, WPATH commissioned a team at Johns Hopkins University in Maryland to conduct systematic reviews.**3435** However, WPATH's recommendations lack a grading system to indicate the quality of the evidence—one of several deficiencies. Both Guyatt and Helfand noted that a trustworthy guideline would be transparent about all commissioned systematic reviews: how many were done and what the results were. But Helfand remarked that neither was made clear in the WPATH guidelines and also noted several instances in which the strength of evidence presented to justify a recommendation was "at odds with what their own systematic reviewers found."

For example, one of the commissioned systematic reviews found that the strength of evidence for the conclusions ormonal treatment "may improve" quality of life, depression, and anxiety among transgender people was "low,"

and it emphasised the need for more research, "especially among adolescents."**35** The reviewers also concluded that "it was impossible to draw conclusions about the effects of hormone therapy" on death by suicide.

Despite this, WPATH recommends that young people have access to treatments after comprehensive assessment, stating that the "emerging evidence base indicates a general improvement in the lives of transgender adolescents."**12** And more globally, WPATH asserts, "There is strong evidence demonstrating the benefits in quality of life and well-being of gender-affirming treatments, including endocrine and surgical procedures," procedures that "are based on decades of clinical experience and research; therefore, they are not considered experimental, cosmetic, or for the mere convenience of a patient. They are safe and effective at reducing gender incongruence and gender dysphoria."**12**

Those two statements are each followed by more than 20 references, among them the commissioned systematic review. This stood out to Helfand as obscuring which conclusions were based on evidence versus opinion. He says, "It's a very strange thing to feel that they had to cite some of the studies that would have been in the systematic review or purposefully weren't included in the review, because that's what the review is for."

For minors, WPATH contends that the evidence is so limited that "a systematic review regarding outcomes of treatment in adolescents is not possible." But Guyatt counters that "systematic reviews are always possible," even if few or no studies meet the eligibility criteria. If an entity has made a recommendation without one, he says, "they'd be violating standards of trustworthy guidelines." Jason Rafferty, assistant professor of paediatrics and psychiatry at Brown University, Rhode Island, and lead author of the AAP statement, remarks that the AAP's process "doesn't quite fit the definition of systematic review, but it is very comprehensive."

Sweden conducted systematic reviews in 2015 and 2022 and found the evidence on hormonal treatment in adolescents "insufficient and inconclusive."**24** Its new guidelines note the importance of factoring the possibility that young people will detransition, in which case "gender confirming treatment thus may lead to a deteriorating of health and quality of life (i.e., harm)."

Cochrane, an international organisation that has built its reputation on delivering independent evidence reviews, has yet to publish a systematic review of gender treatments in minors. But *The BMJ* has learnt that in 2020 Cochrane accepted a proposal to review puberty blockers and that it worked with a team of researchers through 2021 in developing a protocol, but it ultimately rejected it after peer review. A spokesperson for Cochrane told *The BMJ* that its editors have to consider whether a review "would add value to the existing evidence base," highlighting the work of the UK's National Institute for Health and Care Excellence, which looked at puberty blockers and hormones for adolescents in 2021. "That review found the evidence to be inconclusive, and there have been no significant primary studies published since."

In 2022 the state of Florida's Agency for Health Care Administration commissioned an overview of systematic reviews looking at outcomes "important to patients" with gender dysphoria, including mental health, quality of life, and complications. Two health research methodologists at McMaster University carried out the work, analysing 61 systematic reviews and concluding that "there is great uncertainty about the effects of puberty blockers, cross-sex hormones, and surgeries in young people." The body of evidence, they said, was "not sufficient" to support treatment decisions.

Calling a treatment recommendation "evidence based" should mean that a treatment or guideline has not just been systematically studied, says Helfand, but that there was also a finding of high quality evidence supporting its use.

evidence "doesn't just mean something esoteric about study design, it means there's uncertainty about
er the long term benefits outweigh the harms," Helfand adds.

"Evidence itself never tells you what to do," says Guyatt. That's why guidelines must make explicit the values and preferences that underlie the recommendation.

The Endocrine Society acknowledges in its recommendations on early puberty suppression that it is placing "a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm."**14**

WPATH acknowledges that while its latest guidelines are "based upon a more rigorous and methodological evidence-based approach than previous versions," the evidence "is not only based on the published literature (direct as well as background evidence) but also on consensus-based expert opinion." In the absence of high quality evidence and the presence of a patient population in need—who are willing to take on more personal risk—consensus based guidelines are not unwarranted, says Helfand. "But don't call them evidence based."

An evidence base under construction

In 2015 the US National Institutes of Health awarded a $5.7m (£4.7m; €5.3m) grant to study "the impact of early medical treatment in transgender youth."**36** The abstract submitted by applicants said that the study was "the first in the US to evaluate longitudinal outcomes of medical treatment for transgender youth and will provide essential evidence-based data on the physiological and psychosocial effects and safety" of current treatments. Researchers are following two groups, one of participants who began receiving GnRHa in early puberty and another group who began cross sex hormone treatment in adolescence. The study doesn't include a concurrent no-treatment control group.

Robert Garofalo, chief of adolescent medicine at the Lurie Children's Hospital in Chicago and one of four principal investigators, told a podcast interviewer in May 2022 that the evidence base remained "a challenge . . . it is a discipline where the evidence base is now being assembled" and that "it's truly lagging behind [clinical practice], I think, in some ways." That care, he explained, was "being done safely. But only now, I think, are we really beginning to do the type of research where we're looking at short, medium, and long term outcomes of the care that we are providing in a way that I think hopefully will be either reassuring to institutions and families and patients or also will shed a light on things that we can be doing better."**37**

While Garofalo was doing the research he served as "contributor" on the AAP's widely cited 2018 policy statement, which recommends that children and adolescents "have access to comprehensive, gender-affirming, and developmentally appropriate health care," including puberty blockers, sex hormones, and, on a case-by-case basis, surgeries.**15**

Garofalo said in the May interview, "There is universal support for gender affirming care from every mainstream US based medical society that I can think of: the AMA, the APA, the AAP. I mean, these organisations never agree with one another." Garofalo declined an interview and did not respond to *The BMJ*'s requests for comment.

The rush to affirm

Sarah Palmer, a paediatrician in private practice in Indiana, is one of five coauthors of a 2022 resolution submitted to the AAP's leadership conference asking that it revisit the policy after "a rigorous systematic review of available evidence regarding the safety, efficacy, and risks of childhood social transition, puberty blockers, cross sex hormones and surgery." In practice, Palmer told *The BMJ*, clinicians define "gender affirming" care so broadly that "it's been taken by many people to mean go ahead and do anything that affirms. One of the main things I've seen it used for is minimising chest surgery, also known as mastectomy in teenage patients." The AAP has told *The BMJ* that all

policy statements are reviewed after five years and so a "revision is under way," based on its experts' own "robust evidence review."

Palmer says, "I've seen a quick evolution, from kids with a very rare case of gender dysphoria who were treated with a long course of counselling and exploration before hormones were started," to treatment progressing "very quickly—even at the first visit to gender clinic—and there's no psychologist involved anymore."

Laura Edwards-Leeper, a clinical psychologist who worked with the endocrinologist Norman Spack in Boston and coauthored the WPATH guidelines for adolescents, has observed a similar trend. "More providers do not value the mental health component," she says, so in some clinics families come in and their child is "pretty much fast tracked to medical intervention." In a study of teens at Seattle Children's Hospital's gender clinic, two thirds were taking hormones within 12 months of the initial visit.**38**

The British paediatrician Hilary Cass, in her interim report of a UK review into services for young people with gender identity issues, noted that some NHS staff reported feeling "under pressure to adopt an unquestioning affirmative approach and that this is at odds with the standard process of clinical assessment and diagnosis that they have been trained to undertake in all other clinical encounters."

Eli Coleman, lead author of WPATH's Standards of Care and former director of the Institute for Sexual and Gender Health at the University of Minnesota, told *The BMJ* that the new guidelines emphasised "careful assessment prior to any of these interventions" by clinicians who have appropriate training and competence to assure that minors have "the emotional and cognitive maturity to understand the risks and benefits." He adds, "What we know and what we don't know has to be explained to youth and their parents or caregivers in a balanced way which really details that this is the evidence that we have, that we obviously would like to have more evidence, and that this is a risk-benefit scenario that you have to consider."

Joshua Safer, director of the Center for Transgender Medicine and Surgery at Mount Sinai Hospital in New York and coauthor of the Endocrine Society guidelines, told *The BMJ* that assessment is standard practice at the programme he leads. "We start with a mental health evaluation for anybody under the age of 18," he says. "There's a lot of talking going on—that's a substantial element of things." Safer has heard stories of adolescents leaving a first or second appointment with a prescription in hand but says that these are overblown. "We really do screen these kids pretty well, and the overwhelming majority of kids who get into these programmes do go on to other interventions," he says.

Without an objective diagnostic test, however, others remain concerned. The demand for services has led to a "perfunctory informed consent process," wrote two clinicians and a researcher in a recent issue of the *Journal of Sex and Marital Therapy*,**39** in spite of two key uncertainties: the long term impacts of treatment and whether a young person will persist in their gender identity. And the widespread impression of medical consensus doesn't help. "Unfortunately, gender specialists are frequently unfamiliar with, or discount the significance of, the research in support of these two concepts," they wrote. "As a result, the informed consent process rarely adequately discloses this information to patients and their families."

For Guyatt, claims of certainty represent both the success and failure of the evidence based medicine movement. "Everybody now has to claim to be evidence based" in order to be taken seriously, he says—that's the success. But people "don't particularly adhere to the standard of what is evidence based medicine—that's the failure." When there's been a rigorous systematic review of the evidence and the bottom line is that "we don't know,'" he says, then ›dy who then claims they do know is not being evidence based."

Footnotes

- This feature has been funded by the BMJ Investigations Unit. For details see bmj.com/investigations.
- Competing interests: I have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.
- Provenance: commissioned; externally peer reviewed.

References

1. Parker K, Horowitz JM, Brown A. Americans' complex views on gender identity and transgender issues. Pew Research Center's Social & Demographic Trends Project. 2022. https://www.pewresearch.org/social-trends/2022/06/28/americans-complex-views-on-gender-identity-and-transgender-issues/
2. Block J. US transgender health guidelines leave age of treatment initiation open to clinical judgment. *BMJ* 2022;**378**:o2303. doi:10.1136/bmj.o2303 pmid:36167353
3. Respaut R, Terhune C. Number of transgender children seeking treatment surges in US. *Reuters* 2022 Oct 6. https://www.reuters.com/investigates/special-report/usa-transyouth-data/
4. Terhune C, Respaut R, Conlin M. As children line up at gender clinics, families confront many unknowns. *Reuters* 2022 Oct 6. https://www.reuters.com/investigates/special-report/usa-transyouth-care/
5. Johns MM, Lowry R, Andrzejewski J, et al. Transgender identity and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students—19 States and large urban school districts, 2017. *MMWR Morb Mortal Wkly Rep* 2019;**68**:67-71. . doi:10.15585/mmwr.mm6803a3 pmid:30677012
6. Becerra-Culqui TA, Liu Y, Nash R, et al. Mental health of transgender and gender nonconforming youth compared with their peers. *Pediatrics* 2018;**141**:e20173845. doi:10.1542/peds.2017-3845 pmid:29661941
7. Gomez I, Ranji U, Salganicoff A, et al. Update on Medicaid coverage of gender-affirming health services. KFF. 2022 https://www.kff.org/womens-health-policy/issue-brief/update-on-medicaid-coverage-of-gender-affirming-health-services/
8. Littman L. Individuals treated for gender dysphoria with medical and/or surgical transition who subsequently detransitioned: a survey of 100 detransitioners. *Arch Sex Behav* 2021;**50**:3353-69. doi:10.1007/s10508-021-02163-w pmid:34665380
9. Respaut R, Terhune C, Conlin M. Why detransitioners are crucial to the science of gender care. *Reuters* 2022 Dec 22. https://www.reuters.com/investigates/special-report/usa-transyouth-outcomes/
10. Boyd I, Hackett T, Bewley S. Care of Transgender Patients: A General Practice Quality Improvement Approach. *Healthcare (Basel)* 2022;**10**:121. doi:10.3390/healthcare10010121. pmid:35052285
11. Roberts CM, Klein DA, Adirim TA, Schvey NA, Hisle-Gorman E. Continuation of Gender-affirming Hormones Among Transgender Adolescents and Adults. *J Clin Endocrinol Metab* 2022;**107**:e3937-43. doi:10.1210/clinem/dgac251. pmid:35452119
12. Coleman E, Radix AE, Bouman WP, et al. Standards of care for the health of transgender and gender diverse people, version 8. *Int J Transgend Health* 2022;**23**(Suppl 1):S1-259. doi:10.1080/26895269.2022.2100644 pmid:36238954
13. Hadland S. A handful of cruel protesters outside the #AAP2022 meeting, but inside 10 000 pediatricians stand in solidarity for trans & gender-diverse kids & their families to receive evidence based, lifesaving, individualized care between patients, parents & their doctor. @AmerAcadPeds: pic.twitter.com/b2K2JdRnX9. Twitter. 2022. https://twitter.com/DrScottHadland/status/1578815082590400512
14. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: n endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017;**102**:3869-903. doi:10.1210/jc.2017-1658 pmid:28945902

15. Rafferty J, Committee on Psychosocial Aspects of Child and Family Health, Committee on Adolescence, Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. *Pediatrics*2018;**142**:e20182162. doi:10.1542/peds.2018-2162 pmid:30224363

16. American Academy of Child and Adolescent Psychiatry. AACAP statement responding to efforts to ban evidence-based care for transgender and gender diverse. https://www.aacap.org/AACAP/Latest_News/AACAP_Statement_Responding_to_Efforts-to_ban_Evidence-Based_Care_for_Transgender_and_Gender_Diverse.aspx

17. American Medical Association. March 26, 2021: State advocacy update. 2021. https://www.ama-assn.org/health-care-advocacy/advocacy-update/march-26-2021-state-advocacy-update

18. American Psychological Association. Resolution on supporting sexual/gender diverse children and adolescents in schools. 2020. https://www.apa.org/pi/lgbt/resources/policy/gender-diverse-children

19. American Psychiatric Association. Position statement on treatment of transgender (trans) and gender diverse youth. 2020. https://www.psychiatry.org/File%20Library/About-APA/Organization-Documents-Policies/Policies/Position-Transgender-Gender-Diverse-Youth.pdf

20. Boerner H. What the science on gender-affirming care for transgender kids really shows. *Sci Am* 2022 (published online 12 May). https://www.scientificamerican.com/article/what-the-science-on-gender-affirming-care-for-transgender-kids-really-shows/

21. Branstetter G. Transgender youth & health care: a guide for reporters. *Medium* 2019. https://gillbranstetter.medium.com/transgender-youth-health-care-a-guide-for-reporters-820f8fbaff21

22. Olezeski C, McNamara M, Alstott A. Op-ed: Denying trans youth gender-affirming care is an affront to science and medical ethics. *Los Angeles Times* 2022. https://www.latimes.com/opinion/story/2022-06-13/trans-youth-healthcare-state-bans

23. Simmons-Duffin S. Rachel Levine calls state anti-LGBTQ bills disturbing and dangerous to trans youth. *NPR* 2022 Apr 29. https://www.npr.org/sections/health-shots/2022/04/29/1095227346/rachel-levine-calls-state-anti-lgbtq-bills-disturbing-and-dangerous-to-trans-you

24. Socialstyrelsen: National Board of Health and Welfare. Care of children and adolescents with gender dysphoria. Report 2022-3-7799. 2022. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-3-7799.pdf

25. Palveluvalikoima (Council for Choices in Health Care in Finland). Medical treatment methods for gender dysphoria in non-binary adults—recommendation. Jun 2020. https://palveluvalikoima.fi/documents/1237350/22895623/Summary_non-binary_en.pdf/8e5f9035-6c98-40d9-6acd-7459516d6f92/Summary_non-binary_en.pdf?t=1592318035000

26. Académie Nationale de Médecine. La médecine face à la transidentité de genre chez les enfants et les adolescents [Medicine and gender transidentity in children and adolescents. 25 Feb 2022. https://www.academie-medecine.fr/la-medecine-face-a-la-transidentite-de-genre-chez-les-enfants-et-les-adolescents/?lang=en (In French and English)

27. Royal Australian and New Zealand College of Psychiatrists. Recognising and addressing the mental health needs of people experiencing gender dysphoria/gender incongruence. 2021. https://www.ranzcp.org/news-policy/policy-and-advocacy/position-statements/gender-dysphoria

28. NHS England. Implementing advice from the Cass review. https://www.england.nhs.uk/commissioning/spec-services/npc-crg/gender-dysphoria-clinical-programme/implementing-advice-from-the-cass-review/

29. Cass Review. NICE evidence reviews. 2021. https://cass.independent-review.uk/nice-evidence-reviews/

30. NHS England. Interim service specification: specialist service for children and young people with gender dysphoria (phase 1 providers). Oct 2022. https://www.engage.england.nhs.uk/specialised-commissioning/gender-dysphoria-services/user_uploads/b1937-ii-specialist-service-for-children-and-young-people-with-gender-dysphoria-1.pdf

ıstitute of Medicine, Board on Health Care Services, Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. *Clinical practice guidelines we can trust*. National Academies Press, 2011.

https://play.google.com/store/books/details?id=b_RTRs8SE0YC

32. Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, et al. Sex steroids and cardiovascular outcomes in transgender individuals: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2017;**102**:3914-23. doi:10.1210/jc.2017-01643 pmid:28945852
33. Singh-Ospina N, Maraka S, Rodriguez-Gutierrez R, et al. Effect of sex steroids on the bone health of transgender individuals: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2017;**102**:3904-13. doi:10.1210/jc.2017-01642 pmid:28945851
34. Wilson LM, Baker KE, Sharma R, Dukhanin V, McArthur K, Robinson KA. Effects of antiandrogens on prolactin levels among transgender women on estrogen therapy: A systematic review. *Int J Transgend Health* 2020;**21**:391-402. doi:10.1080/15532739.2020.1819505 pmid:34993517
35. Baker KE, Wilson LM, Sharma R, Dukhanin V, McArthur K, Robinson KA. Hormone therapy, mental health, and quality of life among transgender people: a systematic review. *J Endocr Soc* 2021;5:bvab011.
36. National Institutes of Health. The impact of early medical treatment in transgender youth. NIH Reporter. https://reporter.nih.gov/project-details/8965408
37. Northwestern University Feinberg School of Medicine. Evidence-based gender-affirming care for young adults with Robert Garofalo, MD, MPH. 20 May 2022. https://www.feinberg.northwestern.edu/research/news/podcast/2022/evidence-based-gender-affirming%20-care-for-young-adults-with-robert-Garofalo-md-mph.html
38. Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental health outcomes in transgender and nonbinary youths receiving gender-affirming care. *JAMA Netw Open* 2022;**5**:e220978. doi:10.1001/jamanetworkopen.2022.0978 pmid:35212746
39. Levine SB, Abbruzzese E, Mason JW. Reconsidering informed consent for trans-identified children, adolescents, and young adults. *J Sex Marital Ther* 2022;**48**:706-27. doi:10.1080/0092623X.2022.2046221 pmid:35300570
40. Biggs M. The Dutch Protocol for Juvenile Transsexuals: Origins and Evidence. *J Sex Marital Ther* 2022:1-21. doi:10.1080/0092623X.2022.2121238 pmid:36120756
41. Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol* 2006;**155**(Supp 1):S131-7. https://academic.oup.com/ejendo/article/155/Supplement_1/S131/6695708doi:10.1530/eje.1.02231.
42. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al., Endocrine Society. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2009;**94**:3132-54. doi:10.1210/jc.2009-0345 pmid:19509099

Should covid-19 vaccines and drugs be "not for profit"?

○ Yes
○ No

Vote View Results

NHS England

Clinical Policy:

Puberty suppressing hormones (PSH) for children and young people who have gender incongruence / gender dysphoria [1927]

Publication date: 12 March 2024

Commissioning position

Puberty suppressing hormones (PSH) are not available as a routine commissioning treatment option for treatment of children and young people who have gender incongruence / gender dysphoria.

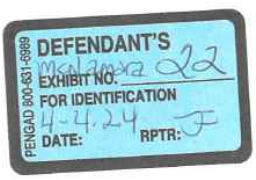
Background

Gender incongruence / dysphoria is a condition where a person experiences discomfort or distress that is caused by a discrepancy between a person's gender identity[1] (how they see themselves regarding their gender) and that person's natal sex (and the associated gender role, and/or primary and secondary sex characteristics).

Diagnostic approaches have been described with reference to the Diagnostic and Statistical Manual of Mental Health Disorders Version 5 published in 2013 (gender dysphoria); and the International Statistical Classification of Diseases and Related Health Problems version 11 effective 2022 (gender incongruence).

The reason why some people experience gender incongruence is not fully understood and it is likely that the development of gender identity is multifactorial and influenced by both biological and social factors. Gender variant behaviours may start between ages 3 and 5 years, the same age at which most typically developing children begin showing gendered behaviours and interests (Fast et al, 2018). Gender atypical behaviour is common among young children and may be part of normal development (Young et al, 2019). Children who meet the criteria for gender incongruence / gender dysphoria may or may not continue to experience the conflict between their physical gender and the one with which they identify into adolescence and adulthood (Ristori et al, 2016).

[1] "Gender" refers to the roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men." [source: WHO website Health Topics: Gender, at https://www.who.int/health-topics/gender]



Gender incongruence / gender dysphoria can become more distressing in adolescence due to the pubertal development of secondary sex characteristics and increasing social divisions between genders. Some studies have found that young people with gender incongruence / gender dysphoria may present to gender identity development services with a range of associated difficulties (e.g. bullying, low mood / depression and self-harm and suicidality).

PSH competitively block puberty hormone receptors to prevent the spontaneous release of two puberty inducing hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. This arrests the progress of puberty, delaying the development of secondary sexual characteristics. In England, the puberty suppressor triptorelin (a synthetic decapeptide analogue of a natural puberty hormone, which has marketing authorisations for the treatment of prostate cancer, endometriosis and central precocious puberty) is one of the puberty suppressing hormones used for this purpose. The use of triptorelin for children and adolescents with gender incongruence is off-label.

In January 2020, a Policy Working Group (PWG) was established by NHS England to undertake a review of the published evidence. As part of this process, the National Institute for Health and Care Excellence (NICE) was commissioned to review the published evidence on Gonadotrophin Releasing Hormone Analogues (GnRHa). Nine observational studies were included in the evidence review (NICE 2020). Overall, there was no statistically significant difference in gender dysphoria, mental health, body image and psychosocial functioning in children and adolescents treated with GnRHa (2020). The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE. There remains limited short-term and long-term safety data for GnRHa. GnRHa may reduce the expected increase in lumbar or femoral bone density during puberty. A re-run of the search was undertaken by NHS England in April 2023 to capture literature published after the NICE evidence review in 2020. Nine further studies were identified.

Current treatments

Treatment of individuals with gender incongruence / gender dysphoria is recommended to be tailored to the specific needs of individual patients and aims to ameliorate the potentially negative impact of gender incongruence on general developmental processes, to support young people and their families in managing the uncertainties inherent in gender identity development and to provide ongoing opportunities for exploration of gender identity (Ristori et al, 2016).

The primary intervention focuses on psychosocial and psychological support; for some individuals, the use of PSH in adolescence to suppress puberty has previously been a treatment option though no NHS clinical commissioning policy has been in place; this may be followed later with gender-affirming hormones of the desired sex (NHS England, 2013). If individuals fulfil additional criteria, they may have various types of gender affirming surgery from the age of 18 years through adult Gender Dysphoria Clinics (NHS England, 2013).

What we have decided

NHS England has carefully considered the evidence review conducted by NICE (2020) and has identified and reviewed any further published evidence available to date.

We have concluded that there is not enough evidence to support the safety or clinical effectiveness of PSH to make the treatment routinely available at this time.

Links and updates to other policies

NHS England has no other policies relating to the sole use of PSH for the treatment of children and adolescents who have gender incongruence.

This document relates to the specialised service for Children and Young People with Gender Incongruence:

- Interim Service Specification for specialist gender incongruence services for children and young people

And to the following policy:

- Clinical commissioning policy for prescribing cross sex hormones

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Gender incongruence	Gender incongruence is where a person experiences discomfort or distress because there is a mismatch between their experienced gender as compared with their assigned sex and its associated physical primary and secondary sex characteristics.

Puberty suppressing hormones	Synthetic (man-made) hormones that suppress the hormones naturally produced by the body and in doing so, suppress puberty, with the aim of reducing the level of puberty-related anxiety in an individual with gender incongruence.
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) is a transparent framework for developing and presenting summaries of evidence and provides a systematic approach for making clinical practice recommendations.

References

World Health Organisation (2018) International Classification of Diseases 11. Available from https://icd.who.int/

Fast, A.A. and Olson, K.R. , Gender Development in Transgender Preschool Children. Child Dev, (2018).89: 620-637. doi:10.1111/cdev.1275

Ristori J, Steensma TD. Gender dysphoria in childhood. Int Rev Psychiatry. 2016;28(1):13-20. doi:10.3109/09540261.2015.1115754

Young, N., Jean, E., Citro, T. (2019). Acceptance, Understanding and the Moral Imperative of promoting social justice education in the schoolhouse. Delaware. Vernon Press p.40

National Institute for Health and Care Excellence (2020). Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria. Available from: Nice Evidence Reviews – Cass Review.