what is in the best interests of the child based on their situation and needs. The requirement for soundness also includes the requirement for compassionate help.

Requirements for investigation

For children and adolescents, it is particularly important to clarify whether the desire for treatment for gender incongruence is stable and not due to other causes. When the consequences of treatment are major and sometimes irreversible, there are stricter requirements for proper assessment. As we have pointed out, the evidence base for the use of puberty-deferring treatment, gender-confirming treatment with hormones and surgery is inadequate. This means that in order to meet the requirement for justifiability, stricter requirements must be set for a thorough investigation when assessing the need for health care. The national guideline does not describe sufficiently clear requirements for assessment and requirements for medical indications for the initiation of treatment. Gender incongruence is not a mental disorder, but a condition that may require both medical and psychological health care. This is particularly true if the gender incongruence has developed into gender dysphoria.

If GI is not a disorder, then why may it require medical and psychological treatments?

If GI leads to GD, treatment may be needed, but do we know what is best?

If GD does exist, psych tx IS NOT needed per current guidelines.

The national guideline states that psychological assessment is not a prerequisite for offering gender-affirming treatment. It is important to avoid pathologizing people with gender incongruence. When the guideline does not set specific requirements for assessment, this can lead to poorer help and care for children and young people. This is a risk, and the study shows that the lack of specific requirements contributes to uncertainty in the services. Health professionals are faced with difficult assessments that require them to consider the potential for harm against what is in the best interests of the child.

Ambiguities and variations in investigation practices

People with gender dysphoria are a heterogeneous group. This makes treatment particularly challenging, both clinically and in terms of research. Several patients, relatives, therapists and administrators have expressed concern about different practices related to the assessment of patients' mental health. Not all people who experience gender incongruence need mental health care, but a significant proportion of the patients referred to the National Treatment Service have current or previous mental illness, developmental disorders or other conditions. People with gender incongruence may also be at increased risk of developing psychological distress, minority stress and sequelae.

> *"In general, the Norwegian Board of Health Supervision is of the opinion that invasive and irreversible measures require a broad differential diagnostic investigation and assessment in order to provide a sound basis for treatment. The requirements for decision-making competence should increase the more extensive the intervention. It is therefore supported that the least invasive gender-affirming treatments should always be considered as the first choice.*
>
> *Furthermore, it is supported that it is important to clarify the need/indication for gender-affirming treatment, risk factors and contraindications, both somatic and mental disorders, in interdisciplinary cooperation."*
> *(The Norwegian Board of Health's consultation response to the draft national guideline for health care for persons with gender incongruence)*

Everyone we have talked to emphasizes the importance of understanding gender incongruence with a biopsychosocial model, i.e. an approach where the whole person is seen and which takes into account physical, psychological and social conditions. Nevertheless, there is disagreement about the content and comprehensiveness of the basic assessment for gender incongruence and gender dysphoria.

In our dialog with stakeholders, we have identified various concerns:

- Concerns have been expressed that the requirement for mental health assessments will prevent or delay help with gender incongruence and lead to unnecessary burdens of extensive assessments of children and young people who do not have mental health problems.

- Many express concern about patient safety because mental health assessments are no longer required. The emphasis is now on avoiding morbidity. This may mean that different mental health

stresses and diagnoses go unrecognized, resulting in children and young people not getting the holistic help they need.

- In addition, concerns have been expressed that a lack of clarity about what constitutes good practice and the discussion around mental health assessment itself means that we are not seeing and acknowledging the whole individual with physical, mental and social needs.

> *"Today, medical practice requires knowledge of biological, psychological and social aspects of gender. Since we only have one word for gender in Norwegian, we have a unique opportunity to think holistically about gender in line with the biopsychosocial medical model." (Slagstad et al. in Tidsskrift for den norske legeforening, February 2023)*

In one of the reports of concern received by Ukom, the relative's child is in his or her early 20s. The young adult is being assessed for gender dysphoria and wants to change her gender from boy to girl. She is following the scheduled plan for assessment for gender-affirming treatment, but apart from this she is not offered or assisted with interviews with a psychologist or follow-up at the district psychiatric center (DPS). Follow-up at the DPS has been rejected due to lack of resources, and that it is not considered necessary health care. The daughter is experiencing an identity crisis, but according to relatives she is left to her own devices and thoughts. It takes three to four months between each consultation. Relatives also believe that both the consultations and the assessment at the DPS were only schematic, which means that the daughter's problems are not picked up. The mother mentions that eating disorders are part of the picture, but that this has neither been treated nor taken seriously.

In practice, we see that there are variations in the mental health assessments carried out by GPs and the specialist health service in child and adolescent psychiatry (BUP) and DPS, before referral to the National Treatment Service. If children and young people with mental illness are on waiting lists without their mental health being adequately assessed or followed up, this may pose a risk to patient safety.

Several people we have spoken to tell us that referrals to BUP have been refused. Gender incongruence is not described in the prioritization guide, Mental health care for children and adolescents. Several from BUP describe that it is demanding to make assessments about prioritizing the group with gender incongruence against other patient groups defined in the guide. In practice, this means that necessary clarifications and assessments regarding mental health can take time and be difficult to coordinate with simultaneous assessments for gender incongruence.

In addition, we see that the time the services currently spend on assessing children and young people with gender incongruence varies. It is also important how close the follow-up is. That is, how frequently/often the person concerned comes in for an interview. Patients and relatives we have spoken to are clear that good and sufficiently close follow-up is absolutely necessary for a safe and good patient pathway. Follow-up during and after the course of treatment is also highlighted as a key need. Gender-affirming treatment can be very demanding to go through.

Consent to healthcare - parental involvement

Our findings show variation in how the competence to consent is interpreted and practiced. There are also challenges in how the child's decision-making competence and parental involvement should be assessed in individual cases. The assessment of competence to consent must be made on an individual basis, and must be based on the child's age and maturity. In addition, the assessment must take into account the nature/type of healthcare. The requirements for consent must be seen in relation to the rules for parents' right to information, cf. patient
- and Users' Rights Act § 3-4.

The general rule is that the age of majority in Norway is 16 years. For persons under the age of 16, it is generally the parents who must consent to health care. In health legislation, there are exceptions in both directions, cf. section 4-3, first paragraph, letters a-c of the Patients' and Users' Rights Act.

For some procedures, parental consent is also required for those over 16 years of age. As examples of this, the Directorate of Health has referred in its circular to the Patients' and Users' Rights Act to participation in research projects or experimental treatment, painful or risky treatment and treatment that is irreversible, including plastic surgery. Some of the treatment provided for gender dysphoria is characterized as irreversible. The guideline on gender incongruence also refers to the need for parental consent for irreversible treatment for persons under 18 years of age. However, the guideline is open to interpretation: *"As a starting point, young people between 16 and 18 years of age cannot therefore decide for themselves on invasive and irreversible procedures".* This does not correspond with what is stated in the circular to the Patients' and Users' Rights Act or with the requirements in the Health Research Act for participation in research projects. Here, there are explicit requirements for parental consent for medical interventions and drug trials on children under the age of 18. We note that there are different requirements for consent in research versus trial/experimental treatment. Gender affirmative treatment is an invasive measure that may affect fertility. The guideline refers to the possibility of storing sperm and unfertilized eggs if one is to undergo treatment that will affect fertility. Reference is made in this context to the Biotechnology Act. This shows the complexity of what children and young people are expected to consider before agreeing to treatment. By way of comparison, we would point out that the age limit for consent to sterilization is 25 years in Norway.

The issue of children's capacity to consent to gender affirmative treatment has been highlighted in connection with a controversial court case in England (Bell vs Tavistock). This has led to an increased awareness of the issue.

The Patients' and Users' Rights Act allows children under the age of 16 (between 12 and 16) to consent to health care without parental involvement. This is linked to the rule on exempting information to parents, cf. section 3-4 of the Patients' and Users' Rights Act. The requirement is that the child/young person has "reasons that must be accepted". In this context, reference is made to conflicts between parents and children, fear of reprisals and that weighty considerations for the patient speak against involving the parents. The national guideline for gender incongruence refers to the same thing, but the guideline is not clear on whether this is also possible even if it involves invasive treatment.

The guideline also allows for information to be withheld from parents even if the child is under 12 years of age, but the guideline specifies that children under 12 years of age cannot consent to health care. Section 4-3, sixth paragraph, of the Patients' and Users' Rights Act states that in cases where information can be withheld from the parents, the person providing health care *"may make a decision on health care that is strictly necessary and that is not invasive in terms of scope and duration. Such a decision may only be taken for a limited period until consent can be obtained."*

The regulations relating to children's capacity to consent and relatives' right to information leave room for interpretation, but the guide to the Patients' and Users' Rights Act provides some clear guidelines on the scope for interpretation. At the same time, the national guidelines for gender incongruence are not as clear. It is difficult to assess children's competence to consent. Competence may vary according to age and maturity and depending on how invasive the measures being considered are. At the same time, there are unresolved questions related to when information from parents can be excluded. The guidelines do not provide clear guidance on these questions.

Several have called for clearer clarification of whether it is justifiable that children under the age of 16 can consent to treatment for gender incongruence and gender dysphoria. In connection with a specific case, the State Governor of Oslo has asked the Directorate of Health for further clarification of the issue.

One of the reports of concern we have received highlights the issue of consent and involvement of relatives. The young person in question is receiving treatment from the primary health service and has informed her parents that she is considering starting gender-affirming hormone therapy. They are in contact with others in the same situation via a treatment center.

Relatives state that their adolescent is in an exploratory phase with a lot of doubt and ambiguity in addition to having mental health challenges. The parents have not received any information or been contacted by the therapist. The parents feel that in a few months their adolescent is in the middle of a new field with many impressions and influences, including new contacts from the treatment center and through social media. They are afraid that they are about to embark on a fast-track treatment that could make them a patient for life. He wants symptom relief in a complex situation, and his parents fear that he is too immature and has too much to cope with to make such a choice in a short time. The parents are concerned that the child may regret the choice later in life and that it will cause harm rather than help.

Parents are the closest caregivers and anchors in a situation that is very demanding for the child, siblings and parents. They want to be a resource and maintain a good relationship with their child, but the family experiences a lack of involvement from the treatment center in the process of their child's exploration of gender identity.

"Involving us parents is to facilitate good relationships for the rest of our lives."

MOR

Assessing capacity to consent can be challenging. It is therefore all the more important to involve relatives. There is a clear expectation in the current regulations that relatives should be involved unless there are compelling reasons to the contrary.

The assessment and treatment of children and adolescents with gender incongruence and gender dysphoria is complex. The fact that they are undergoing intense physical and psychological development must be taken into account. If children and adolescents are to be able to consent to gender-affirming treatment on their own, it is unclear what it takes to say that the child is mature enough to make such a decision. What requirements should we set in order to assume that the child has sufficient understanding and insight to understand the consequences of the choices made? In addition, there is the question of what information must be available to make the choice. The law sets clear requirements for information to all patients receiving health care. This includes information about their state of health, the content of the healthcare and any risks and side effects. This knowledge is important in order to make informed choices. As we have discussed in the evidence base, we know little about the long-term effects of puberty blockers and side effects of hormone treatment.
Patients need to be informed about this and understand the consequences of their choices. Meeting and talking with the healthcare provider will be crucial for the choices to be made by children and young people.

> *"It is important that this patient group is met in an open and non-judgmental way so that they feel safe and cared for. In our experience, it is very difficult to balance helping patients to arrive at a definite position that gender-affirming measures are what they want, which will often involve probing questions, against making them feel cared for and understood. When the issue is one's own identity, it is easy to fall into the trap of offending."*
> *(Consultation statement Norwegian Association of General Practice, Norwegian Medical Association)*

In summary

Our findings show that it is questionable whether all children and adolescents with gender incongruence and dysphoria receive appropriate health care. Children's right to consent to health

care and parents' right to information are challenging issues for health personnel to consider. Children and adolescents may have different degrees of physical and mental maturity and may be at different levels of development despite being the same age. If children and

young people should be able to consent to gender-affirming treatment on their own, it is unclear what it takes to say that the child is mature enough to make such a decision.

The guideline does not require an assessment or a medical indication for the start of treatment. The guideline does not function well as a professional standard and constitutes a patient safety risk in its current form.

9 Our findings: Right to health care - a gap in expectations

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The guideline on gender incongruence pays great attention to the patients' right to health care. The right to necessary health care from the municipal health and care services and the specialist health service is laid down in the Patients' and Users' Rights Act. The concept of "necessary health care" is interpreted as giving a right to (necessary) health care of an acceptable standard based on an individual assessment of need. The scope and level must therefore be assessed specifically on the basis of a health professional assessment of the patient's needs.

The requirement of soundness should always be decisive in assessing the patient's right to healthcare. The right can be related to the municipal health services and to the specialist health services.

The national professional guideline is not clear on the level of assistance to be provided once a medical assessment of need has been made. It is left to the service to define who is entitled, what they are entitled to and when they are entitled to different health services. What is considered specialist health care and what services can be provided by the municipal health service is also not clearly defined. This is more or less left to the services to define based on an assessment of justifiability.

In order to be entitled to healthcare from the specialist health service, some specific requirements must be met. Firstly, the right is linked to a medical assessment of the patient's need for specialized health care. The guideline does not say anything about what should be included in a medical assessment of the need, but that it must be based on a proper assessment of the patient. The guideline states that gender incongruence in itself does not provide grounds for referral to the specialist health service, but there may be a risk of developing a mental disorder. People with gender incongruence may have gender dysphoria, a condition that causes psychological pain, discomfort or other complaints that require health care. It is the individual's need that determines whether they are entitled to health care and the level of care they should receive.

The Prioritization Regulations elaborate on the assessments that are relevant for determining who is entitled to necessary health care from the specialist health service. In the individual assessment of the patient's entitlement, the expected benefit of the health care must be assessed. The expected benefit of the healthcare is assessed on the basis of whether evidence-based practice indicates that

the healthcare can increase the patient's life expectancy and/or quality of life. It must be assessed whether the health care product can increase the probability of: survival or reduced

loss of function, physical or mental improvement of function, reduction of pain, physical or mental discomfort, cf. the Priority Regulation.

As described above, little is known about the long-term effects of puberty-delaying treatment and gender-affirming treatment with hormones. There is a need for more research to be able to say something about short- and long-term effects. It is therefore also difficult to say anything about the expected benefit of the treatment as long as we do not have a sufficient knowledge base.

The right to necessary health care does not include experimental or test treatment, cf. Circular I-4/2019. Experimental treatment means all treatment where efficacy and safety have not been sufficiently documented for the treatment to be included in the ordinary treatment offer. Investigational treatment covers both treatment tested in clinical trials and treatment provided outside clinical trials, but the general rule is that investigational treatment should be provided through clinical research studies. The national principles allow for treatment that is not based on sufficient documentation to be given to individuals outside clinical trials in exceptional cases when this is professionally justifiable. This is stated in the Directorate of Health's guidelines for investigational treatment. It also states that although the principles for experimental treatment were developed for the specialist health service, they can also be used as a basis for the use of experimental treatment in the municipal health and care services.

This means that there is room for maneuver to offer investigational treatment, but it is a fundamental prerequisite that the offer of investigational treatment is assessed as justifiable. The justifiability requirement is a legal standard that changes in line with medical and technical developments, but the core is linked to what is defined as established treatment at any given time. When there is no established treatment option, it is particularly important to have a safe framework for the treatment. Treatment must then take place within a predictable framework and contribute to increasing knowledge. This is particularly important for the group of teenagers with gender dysphoria who are increasingly seeking the health services for puberty delaying and gender affirming treatment where the research-based evidence base is inadequate.

It is the health authorities that decide what should be available in the service. This is based on a thorough assessment of the available knowledge about the service. Knowledge is obtained, among other things, through HTAs. A full HTA involves a comprehensive systematic assessment of new or established methods in which efficacy, safety and/or cost-effectiveness are reviewed and assessed. The assessment often also includes questions concerning ethical, legal, organizational and societal consequences.

The national guideline on gender incongruence does not use the concept of experimental treatment and bases the right to necessary specialist health services on experience-based knowledge. This is not consistent with other help provided by the specialist health service. The prioritization regulations stipulate that the patient should benefit from the health care and that the assessment of benefit requires evidence-based practice. The national guideline also points out that evidence-based practice is inadequate and highlights a prerequisite when describing the main elements of evidence-based practice:

> *"It is possible to develop evidence-based recommendations with more emphasis on clinical experience and user knowledge while awaiting research-based documentation, as has been done in this guideline. This assumes that health care will be followed by systematic collection of data for research. The basis for making clinical decisions will thus be better in the time to come."*

This lack of connection between the right to health care and ambiguities in the evidence base means that the health authorities must make a thorough assessment of the justifiability in the light of the available evidence base. They must make this assessment before deciding which services to provide. It will therefore be demanding for the regions to put in place an assistance and treatment

service.

Gender-affirming treatment is ongoing among different actors in Norway. No national register has been established, nor have there been specific requirements or resources allocated for follow-up research with systematic data collection. The knowledge base is thus not strengthened to make better clinical decisions locally at the individual practitioner, regionally or nationally. By defining treatment with puberty blocks, gender-affirming hormone therapy and surgery for children and adolescents as experimental treatment, there will be stricter requirements for a predictable framework for the help. This will contribute to safer and more predictable services. The framework will also contribute to increased knowledge.

Different expectations

Our investigation indicates that there is a gap between what the guideline outlines and what is possible given the current available services and knowledge base. When the national guideline states that people with gender incongruence are entitled to health care, without the evidence base being well documented and without a good overview of any negative aspects of the treatment, an expectation is created among patients that the services can hardly meet.

This relates both to expectations of the health service and its organization. Parts of the patient population have an expectation that the right to treatment should be fulfilled on the basis of a subjective need. It thus becomes a source of frustration when the Norwegian health system is organized in such a way that requirements for expected benefit, efficacy and safety are what trigger the type of help and treatment.

For many people with gender incongruence, it can be difficult to know what the right help and treatment options are. Here, as elsewhere in the service, the GP will first have an important function in helping the person to find the right health care and then as support during the treatment and after the treatment is completed. The GP has a gatekeeper function in the Norwegian health service, and this is important for patient safety in order to avoid overtreatment, among other things. In our study, we see that some actors in this field use the gatekeeper model as an argument for discrimination. The role of the GP in relation to access to specialist health services applies across patient groups. The role can be challenging to manage, especially when unclear frameworks or criteria for treatment meet clear patient expectations. There is a need to clarify the framework for care and treatment and to align expectations.

Health personnel have also told us that it is difficult to relate to the expectations of rights in a field where they are faced with difficult ethical considerations between "doing good" versus "doing no harm". Ukom has been told by health personnel that gender incongruence is a field that many are reluctant to enter because of the fear of doing more harm than good.

In summary

We see that when the evidence base is insufficient, the right to health care creates conflicting expectations and demands. One consequence of this is that some patients feel that they are not seen and heard. There is a great need to harmonize expectations and opportunities in patient care for children and adolescents with gender incongruence and gender dysphoria. It must then be considered whether the interventions require a framework that meets the requirements for experimental treatment.

It is important to make the necessary clarifications at system level to reduce the gap between expectations and practice. Expectations that are not met are burdensome for patients and their families and create ethical dilemmas for those working in the service.

10 Our findings: Performance climate and interaction

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Discrimination and the fight for rights has been an ongoing issue within the trans community. Patient and family organizations and professionals have been active in advocacy work, demanding better patient services and various measures to prevent discrimination against trans people in the health services. This has gone hand in hand with important work aimed at promoting the rights of trans people in all sectors of society.

Performance climate and development of health services

Diversity and inclusion are also key issues in the ongoing debate about the treatment of people with gender incongruence and gender dysphoria. The debate about whether the health service is inclusive and what constitutes good practice is ongoing in the media, social media and within the health service. In our review of the debate, we see that it is sometimes unbalanced and highly polarizing.

This leads to several simplistic messages that are very unfortunate for the field of gender incongruence in terms of establishing a comprehensive and equal health service for those in need of help and treatment.

A climate of expression has developed that is characterized by polarization and harsh, judgmental language. The Freedom of Expression Commission, which delivered its report in 2022, highlighted the debates on gender diversity and gender expression as an area where social condemnation can be high for those who choose to express themselves.

"Those who enter the debates risk being labeled as phobic, prejudiced, hostile or reactionary"

THE FREEDOM OF EXPRESSION COMMISSION

Furthermore, the Freedom of Expression Commission writes that this will limit the real freedom of expression for others, including those who wish to contribute new or different perspectives, facts and opinions. Empathy, the ability to put oneself in the shoes of others, requires a common space for conversation where everyone has the opportunity to participate.

Our report points out that work remains to be done to put in place a differentiated health service that addresses the different needs of gender incongruence. A health service must embrace the gender diversity that exists in society. To succeed in this, it will be important to establish a climate of cooperation in order to further develop the health services. Our survey shows that parts of the current dialogue from some actors are characterized by ideology and an us-versus-them rhetoric. Ukom is concerned that the current discourse and level of conflict inhibits rather than promotes the development of sound health services and treatment options.

In recent decades, there has been a major focus on and further development of patient, user and family participation in the health service. We believe that in the future it is important to use the established systems and methods that have been developed nationally and internationally as a framework for cooperation. User participation at system level can contribute to increased accuracy and quality, both in service development and research. The Norwegian Directorate of Health is working to develop national professional advice for user participation in the field of substance abuse and mental health, with the aim that these can eventually be further developed for the entire health and care service. The project highlights these benefits at the system level:

- User and family knowledge is understood and used as an equal area of knowledge in service development, implementation and evaluation at system and service level.
- User and carer organizations, user-run centres, experience consultants and other patient and user voices have a common understanding of each other's roles and responsibilities.
- Staff and managers in the services facilitate increased user and family involvement.

These points are also good for highlighting some of the conditions for a genuine and respectful climate of cooperation:

- Stakeholders have a responsibility to see each other as equal partners with important knowledge to develop services.
- Stakeholders have a responsibility to establish a common understanding of each other's
- roles and responsibilities. The service is responsible for facilitating increased user and family involvement.

Effects of a harsh climate of expression

We have found that the debate taking place in the media and on various social networks affects those with gender incongruence and gender dysphoria, their families and those working in the field. The debate is characterized by sometimes major and fundamental differences of opinion. Particularly prominent is the discussion about what treatment should be offered to young people with gender

incongruence and gender dysphoria.

We have found that the debate and disagreements affect four areas in particular that can compromise patient safety. It affects:

- the relationship between patient and carer/treatment provider
- access to information
- participation in the debate
- recruitment/engagement in the field

Relationship and alliance building between the therapist/helper and the person seeking help/treatment can be affected by disagreements and differing expectations. Conversations and assessments that help to find the right help for the individual require a safe and open climate for expression. It is demanding to build security, trust and alliances in a landscape of uncertainty, distance and fear. We find that within gender incongruence, both trust in therapists and in treatment institutions is affected by a debate about what is good practice in the treatment of gender dysphoria.

In general, it can be difficult for children and young people to find relevant health information. In particular, it can be difficult for children and young people to deal with conflicting messages from professionals and from discussions on the topic in social media. At times, we see that messages about help and treatment for gender incongruence are not very nuanced, and it is difficult to get an overview of the risks and benefits of the treatments.

"We don't talk about side effects very much. There's talk of "as long as I get hormones, my body will go in the direction I want". I think it's important that we have a balance here. The fact that you have side effects, or that you are struggling, does not mean that this is wrong."

REPRESENTATIVE PATIENT ORGANIZATION

"We also need to look at hormones. It can create pleasure and serious side effects. Blood clots and so on. There are also many people I meet who don't understand the seriousness of side effects. This is something that not only affects you on the outside, but also on the inside"

REPRESENTATIVE PATIENT ORGANIZATION

The use of harsh and judgmental language carries the risk that some people may be reluctant to participate in public debate. For some, it may be too challenging to participate and express themselves because they have opinions that they know will not be tolerated by everyone. In this climate of expression, the cost of participating in public discourse with opinions or expertise may be too high.

"So polarized a debate that even as a patient, I risk being verbally trampled - caught in having to choose sides. Like a divorce debate."

PREVIOUS PATIENT ASSESSMENT/TREATMENT GENDER INCONGRUENCE

Recruitment of clinicians and researchers to the field is affected by the debate. The fierce debate may also make practitioners reluctant to work in the field for long periods of time. Professional disagreement and lack of consensus can also increase the burden on practitioners, and a pressured work environment can compromise patient safety.

"This is a very demanding field to work in. Unfortunately, the polarization means that we just stand and bump into each other instead of improving the field. I have a friend who works in the BUP system, and in relation to this topic she says: I go to work, and almost no matter what I do, I make mistakes."

TREATMENT

"Polarization is blocking research."

PRACTITIONER AND RESEARCHER

Fear

The word fear has been repeated by several stakeholders in our survey. Children and young people are afraid of not being believed and understood, and many are afraid of not getting the help and treatment they need. We have been told by several young people who are being examined for gender incongruence that they answer what they think is expected. Young people also share their experiences on social media, and they can get information on how best to respond in order to access gender-affirming treatment.

Relatives are afraid that their child will not receive the right health care, and they point to the many influences, complexities and climate of expression that make this particularly difficult. Relatives also report that they are afraid to express their concerns and uncertainty about the invasive treatments for fear of being labeled as transphobic. They express that they want to be supportive and caring. Relatives also mention that friends and close family members may avoid asking critical questions to

their young person for fear of hurting their feelings.

Practitioners report that they are afraid of offending, afraid of ignoring other illnesses or giving treatment for which they are not fully aware of the effects or consequences, and in particular they are afraid of causing harm or not providing proper health care. They express concern about overtreatment, for example, starting hormone treatment unnecessarily or too quickly, or the treatment period with puberty blockers being too long. They also express concern about malpractice, for example when they have to take over the assessment, treatment and follow-up of children and young people who have started treatment on their own or with other practitioners on varying grounds. One practitioner in the field has recently lost his license for various reasons, and media coverage has conveyed much fear in this regard.
Professionals with different perspectives at different levels of the health service report that they receive harassment and threats, but in conversations with Ukom, these different actors have been primarily concerned with patients, patient safety and soundness. Although the conditions can be demanding, practitioners in the health service also report a lot of support and good patient relations. Several patient organizations and professionals also express concern about undertreatment and the consequences of this if the decentralized service is not put in place. Many are afraid that the outcome of the ongoing debate on accountability will be a reduction in treatment services.

In summary

The climate of expression in this field in the public domain affects the available information for children and young people with gender incongruence and gender dysphoria and their families. There is a massive impact on children and young people in different communities, also related to treatment and health services. There is a lot of fear and anxiety about getting it wrong from all sides. Different opinions about what is the right treatment can lead to difficult cross-pressures. Different emphasis and discussion of what is necessary at group level can confuse and undermine patient-provider relationships and a personalized approach for the person concerned.

We would like to emphasize that all actors have a shared responsibility for good coordination. The field needs to establish a constructive community for everyone involved in good health care for people with gender incongruence and gender dysphoria. This could make it easier for clinicians and researchers to seek out the field and, not least, for children and young people and their families to seek the help they need.

In addition, interested and affected parties need quality-assured information on the treatment options for gender incongruence and current knowledge on efficacy and safety. This information needs to be accessible and adapted to different target groups, including children and young people.

11 Our recommendations

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Our survey shows that there are major differences in the health services for children and adolescents with gender incongruence and gender dysphoria. Actors in the health services have different understandings of the knowledge base and different assessments of what constitutes acceptable health care. This has led to a situation with variation in the treatment offered, where patients may encounter different expertise and different approaches to assessment and treatment depending on which provider they seek help to manage their gender incongruence and gender dysphoria. It is now important to strengthen the help provided in the municipalities, the specialist health service throughout the country and the national treatment service.

We see that the national guidelines leave too much room for different interpretations, which has resulted in variations in the treatment offered to children and young people. When the authorities decide to grant a group the right to health care, this must be based on a thorough assessment of need, justifiability, cost and benefit. The guidelines must provide the services with the necessary guidance and be a tool for professional standardization that the services can use to ensure that patients receive appropriate and equal health care throughout the country. The evidence base for the treatment of gender incongruence and gender dysphoria is inadequate. This is particularly true for the teenage population, which accounts for a large part of the increase in referrals to the specialist health service over the last ten years. The stability of gender dysphoria that occurs or is expressed in the teenage years is not known. It is also true for patients with non-binary gender incongruence and gender dysphoria.

Against this background, UCOM's recommendations relate to revising the guideline, ensuring a safe framework for the treatment offered and measures to strengthen the evidence base. The recommendations will also ensure systematic data collection and promote follow-up research. It is important that children and young people with gender incongruence and gender dysphoria, including non-binary people, are properly cared for while health services are being developed.

1. Revising the national professional guideline on gender incongruence

Ukom recommends that the Ministry of Health and Care Services commission the Norwegian Directorate of Health to revise the national guideline on gender incongruence. The revision must be based on a systematic review of the evidence.

The following should be included in an audit:

- clarify which treatments can/should be done by primary care, what can/should be done at regional level and what should be done by the national treatment service clearer professional
- guidelines and recommendations for the content of the assessment
- clearer professional criteria for the initiation and completion of treatment
- concrete guidelines for clinical issues that may arise during the course of assessment

and treatment, including specifications on indications and contraindications clearer requirements for the follow-up of patients before, during and after the end of treatment

- clearer guidance on when and how relatives should be involved in the assessment and treatment process
- clearer guidance on how services should address issues of competence to consent in children and young people seeking treatment for gender incongruence and gender dysphoria
- clearer guidance on the skills required by services to assess and treat children and young people with gender incongruence and gender dysphoria
- clearer guidelines for the care of all people with gender incongruence and gender dysphoria, regardless of whether or not highly specialized treatment is appropriate

A systematic review will also contribute to a common platform, language and terminology for the different actors involved in the field. A systematic review can build on recent reviews from abroad.

2. Ensuring a safer environment for the treatment of children and young people

In order to improve the basis for making clinical decisions, it is a prerequisite that health care and treatments are followed by systematic collection of data for quality assurance and research. Clinical research aimed at improving quality and patient safety is in line with the National Action Plan for Clinical Trials and is necessary in this field. This will help to ensure a safe framework for the treatment and follow-up of children and young people until the knowledge base on efficacy and safety is sufficiently documented.

Ukom recommends that puberty blockers and hormonal and surgical gender affirming treatment for children and adolescents be defined as investigational treatment. This is particularly important for teenagers with gender dysphoria.

3. Strengthening the knowledge base - National Medical Quality Registry

Our findings show that the knowledge base is insufficient, and we therefore make several recommendations that together will help to strengthen the knowledge base.

We believe that there is a need to establish a medical quality registry with national status. We consider that the treatment of children and adolescents with gender incongruence and gender dysphoria meets the criteria for establishing a national medical quality register. According to the Norwegian Directorate of Health's national guidelines for approval of medical quality registers for national status, a lack of professional consensus on diagnostics and treatment may be grounds for prioritizing the establishment of a medical quality register with national status.

Ukom recommends that the Ministry of Health and Care Services consider whether a national medical quality register should be established for the treatment of children and adolescents with gender incongruence. Necessary measures must be taken to ensure that such a national quality register can be established, operated and financed in order to contribute to an overview, improve quality and reduce unjustified variation in patient treatment.

12 Procedure for the survey

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In the spring and summer of 2022, Ukom received two reports of concern from relatives of adolescents and young adults with gender incongruence. The reports of concern provided the basis for going into the topic of gender incongruence in more detail. We have not examined a specific patient history, but we have gathered information from various people with gender incongruence and gender dysphoria. In line with the guidelines in the Act on the National Commission of Inquiry for the Health and Care Services, we have omitted all personal names in the report.

Information base

Our assessments are based on information from interviews, dialog meetings and public documentation. We have obtained the status of treatment of gender incongruence from the four regional health authorities. We have reviewed statistics, professional literature, research and followed available public debate and media coverage. We have shared experiences with the Healthcare Safety Investigation Branch (HSIB) and their report on the same topic.

We have also engaged with various experts and resource persons at different stages of the process.

Collection of data

We initially started a mapping exercise on the topic. The review and systematization of the collected written documentation was the starting point for some main themes and questions we wanted to elucidate further in interviews and dialogue with various stakeholders.

Conversations and semi-structured individual interviews were conducted with four patients and two relatives. These were people who had personal and family experience with gender incongruence and gender dysphoria.

Our interviews are based on the K.R.E.A.T.I.V. method, which aims to obtain the most reliable information possible from the informants.

During the information gathering phase, we held dialogue meetings with the following patient, user, next of kin and interest organizations: FRI - The Association for Gender and Sexuality Diversity, Genid, Harry Benjamin Resource Center (HBRS) and the Patient Organization for Gender Incongruence (PKI).

We also held dialog meetings with different treatment environments and levels: The National Treatment Service for Gender Incongruence (NBTK) at Oslo University Hospital HF, the Health Center for Gender and Sexuality (HKS) in Oslo Municipality and the four regional health authorities (RHF) through their technical directors and staff. In addition, we had meetings with the Directorate of Health (Hdir), the Norwegian Board of Health Supervision (Htil) and the Norwegian Institute of Public Health (FHI). In total, we had 11 meetings during this phase, where we presented topics and

presented concerns reported to Ukom.

The different actors decided who and how many people they wanted to bring to the meeting. Some of the meetings were fully digital, some of the meetings were physical, and some of the meetings were hybrid meetings with a large variation in the number of participants. In one hybrid meeting, not everyone who was connected digitally attended the entire meeting.
The interviews were in principle semi-structured with an emphasis on open, exploratory questions. All meetings began with a presentation by Ukom and ended with an open discussion afterwards. Meeting participants chose what they wanted to comment on or raise first. Ukom had a list of topics we wanted to highlight. At meetings with many participants, it was necessary to actively manage the meeting to ensure that more people were allowed to speak and that the desired questions were answered. At other meetings, where only one or a few people attended, they were allowed to speak more freely as long as the requested topics were covered. No audio recordings were made, but notes were taken. The meetings were always attended by several people from Ukom with different professional backgrounds.

We also held five exploratory discussions with professionals with legal, medical, sexological and administrative expertise. In addition, we consulted with people with experiential and relevant professional expertise as needed.

Analytical work

We have sorted and analyzed the collected data to find possible connections, influences and causes of what may constitute a patient risk in the health services for children and adolescents with gender incongruence and gender dysphoria. When we enter a topic to shed light on patient safety, the picture will be complex and the causes of possible risks will be interdependent.

Ukom uses security methodology to identify underlying causes at the system level. As a basis for those parts of the analysis, we have used the Sociotechnical approach, with MTO (human-technology-organization) keywords and methodology, AcciMap methodology, causal maps, actor maps and influence diagrams. This methodology highlights how relationships at different organizational levels influence each other. This approach provides a holistic understanding of possible causal relationships at different levels. We looked at how different services and systems relate to each other, and we have formulated and tested hypotheses along the way.

Validity requirements

In order to come up with recommendations that could be useful for this field and this group of patients, we have conducted dialog meetings and anchored our findings with all stakeholders who have provided us with valuable feedback and input.
During the course of the survey, we have also received useful input from UCOM's reflection panel.

All informants have been given the opportunity to review any quotes we have used.

All are anonymized. Those quoted have been involved in shaping how they are referred

to. Stakeholders involved have also been presented with findings and themes for

recommendations.

Furthermore, findings and draft recommendations have been discussed with informants, user organizations, other interest groups, professional organizations, businesses and professional communities in both the clinical and research fields, the administration, authorities and individuals with special knowledge of the topic.

In this phase, we conducted 11 dialog meetings with the following bodies:

- Norwegian Nurses' Association (NSF)

- Norwegian Psychological Association (NPF)
- The Norwegian Medical Association (DNLF) Patient
- Organization for Gender Incongruence, PKI
- Association for Gender and Sexuality Diversity Free, with Queer Youth

- Genid Norway
- Patient organization and user organization Harry Benjamin Resource Center
- National Association for Relatives in Mental Health
- Mental health
- Patient and user representatives
- National Treatment Service for Gender Incongruence
- (NBTK) Health Center for Gender and Sexuality (HKS), Oslo
- Municipality The regional health authorities
- Directorate of Health
- Norwegian Board of
- Health Supervision
  Norwegian Institute of
  Public Health (NIPH)

In total, we held 27 meetings with various stakeholders during the survey. In these meetings, we have openly discussed the issues and findings and asked for input. In addition, we have allowed for written input afterwards, which several stakeholders have taken advantage of.

PATIENT SAFETY FOR CHILDREN AND YOUNG PEOPLE WITH GENDER INCONGRUENCE

13 Glossary of terms

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This list is taken from Bufdir's Lhbt+ glossary. The terms can be defined in several different ways, and the terminology in the field is constantly evolving. Therefore, some terms may be inclusive to some, but alienating to others.

Non-binary

A person who does not feel that they fit into the categories 'male' or 'female'. Being non-binary is about gender identity and not about what the body looks like. Some non-binary people identify as something in between female and male, others do not identify by gender. In society, gender is often divided into two categories, girl and boy. This division does not apply to everyone

Gender

Gender is often a fundamental aspect of a person's identity. Societal norms play a large part in defining what is typically female and male. What is seen as male and female varies throughout history and between cultures.

Gender can be understood as three different aspects: biological gender (the body you are born with), psychological gender (the gender you feel you are) and social gender (the gender others perceive you as and into which you are socialized).

It is commonly thought that there are two genders, male or female. However, there are people who do not feel at home under these two categories. Therefore, in some countries there is a possibility to register as a gender other than male or female.

- **Biological sex:** Biological sex is made up of biological factors such as external and internal genitalia, genes, chromosomes and sex hormones.
- **Legal gender:** Society's official registration of gender. Legal sex is the sex with which you are registered in the National Population Register. Legal gender does not necessarily correspond to social gender. The Act on Change of Legal Gender came into force in 2016. Under this law, you decide for yourself whether you are listed as a woman or a man in the National Population Register. If you are 6 years old or older, you do not need a medical certificate to change your legal gender. The law applies to people who have reached the age of 16, but people aged between 6 and 16 can apply to change their legal sex with the permission of their parents. Children under the age of 6 can have their legal sex changed if they have a congenital, uncertain somatic gender development. The condition must be documented by a health professional. It is the tax office that decides on the change of legal gender status and assigns a new national identity number.
- **Social gender:** The gender others perceive you as and into which you are socialized.

Gender identity

Gender identity refers to a person's internal experience of being female, male, both female and male, or neither. Most people identify with the sex they were assigned at birth, but not all. Perceived gender can be used as a synonym for gender identity.

Gender expression

A gender expression is the way we identify ourselves as either female, male, feminine, masculine or outside of society's two-gender norm. Although most people present themselves in a gender expression that is perceived as clearly male or clearly female, some people have a gender expression that breaks the dichotomy between male and female.

Gender affirmative action

Health care that helps confirm a person's gender identity. For people who experience discomfort with the mismatch between biological sex and gender identity, this healthcare can be important to improve their quality of life. It may include psychosocial support/care, assistive devices (such as wigs or voice training), sex hormone supplementation or surgical procedures (such as breast removal or vaginal reconstruction). Gender-affirming treatment helps to alleviate gender dysphoria and to enable a person to function in accordance with their gender identity.

Gender dysphoria

Gender dysphoria is a medical term for discomfort caused by a mismatch between a person's gender identity and the sex assigned at birth and the gender role associated with this. Gender dysphoria is a term within the gender incongruence spectrum. People who experience gender dysphoria may wish to undergo gender-affirming treatment to align their body with their gender identity. Not all trans people experience gender dysphoria

Gender incongruence (transgender people)

Gender incongruence is the persistent experience that the gender assigned at birth does not match the gender you perceive yourself to be. People with gender incongruence are often referred to as transgender people. Not all people who experience gender incongruence define themselves as transgender. Gender incongruence is also a diagnosis that replaces all diagnoses that previously began with
"trans"- and is explained as a mismatch between perceived gender and the gender assigned at birth.

Gender characteristics

Sex characteristics refer to the biological or bodily aspect of gender, i.e. physical features, sex chromosomes, sex hormones and genitalia. Individuals with variation in bodily sex development are born with a combination of sex characteristics that vary to a greater extent than we traditionally associate with male and female bodies. Sex characteristics can be divided into primary and secondary sex characteristics:

- **Primary sex characteristics** include sex chromosomes (e.g. XX, XY, X, XXY), external genitalia (e.g. head of penis, foreskin, clitoris, labia, vulva), gonads/sex glands (testes and ovaries), hormones (estrogen and testosterone) and internal reproductive organs (e.g. uterus, fallopian tubes, prostate).
- **Secondary sex characteristics** are characteristics that develop later in life, often around puberty, and can be linked to hormonal development. These may include body and facial hair, menstrual cycle, breast development, height, muscle distribution and body fat

Gender diversity

Gender diversity refers to the fact that there are many ways of being a woman/man or boy/girl, including gay, straight, lesbian, bisexual and transgender people. The term also opens up the possibility that there are more gender identities than woman and man. The term can help to create space for different gender expressions,
-preferences and identities without categorizing.

LGBTQ

Lhbtiq is an abbreviation for lesbian, gay, bisexual, transgender, gender variant/intersex and queer. The term Lhbtiq encompasses terms related to sexual orientation (lhbq), gender identity (t) and gender characteristics (i).
The term "people who transgress gender and sexuality norms" is the most precise and least exclusionary term for this group.

Minority stress

Minority stress is the additional burden that individuals from stigmatized groups face because of their minority position.

Gender and sexuality norms

Norms are unwritten rules, thoughts and ideas that a society, and we who live in it, take for granted. Norms create expectations of how we should behave and what we should be like and involve ideas about what is positive and what is negative. Norms vary between societies and cultures and can change over time. Gender norms are widespread beliefs that assume that everyone identifies with the gender they were assigned at birth and that our behavior and how we express ourselves corresponds to this gender. Norms of sexuality revolve around expectations about who we are attracted to, fall in love with, have sex with, how we have sex and what turns us on. In a heteronormative society, it is assumed that everyone is heterosexual

Skewed

Skeiv is a Norwegian translation of the English term 'queer'. Many people use "queer" as an umbrella term for anyone who breaks gender and sexuality norms, or as a synonym for lhbtiq. For others, 'queer' is an identity that challenges and transcends the categories of heterosexual, lesbian, gay and bisexual and involves a critique of society's heteronormativity. Queer is also used by people who feel that they do not fit into society's division of people into two genders. Not everyone is comfortable with the word 'queer' being used about them.

PATIENT SAFETY FOR CHILDREN AND YOUNG PEOPLE WITH GENDER INCONGRUENCE

14 Ukom's mission

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The National Commission of Inquiry for the Health and Care Services (Ukom) is an independent, governmental body tasked with investigating serious incidents and other serious matters in the health and care services in Norway.

Ukom will investigate the course of events, causal factors and causal relationships. The purpose of the investigations is to improve patient and user safety through learning and prevention of serious incidents.

Ukom does not take a position on civil or criminal guilt and liability.
Ukom decides which serious incidents or serious circumstances are to be investigated, the timing and scope of the investigation and how it is to be carried out.

The surveys are carried out in consultation with stakeholders, i.e. health and social care professionals, patients, users and relatives.

The reports from Ukom are public and do not contain references to individual names and addresses. It is assessed in each individual investigation whether reference is made to the location of the incident.

Ukom's activities are authorized in the Act on the National Commission of Inquiry for the Health and Care Services of 16.06.2017 no. 56.

15 Reference list

Published on March 9, 2023 Last updated on March 9, 2023

We have reviewed a large body of literature and we refer here to a selection of references. This is not a systematically complete list of available literature and references. We have included references highlighted by resource persons with expertise and through dialog meetings.

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Pubertal Suppression, Bone Mass, and Body Composition in Youth With Gender Dysphoria

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abstract

BACKGROUND AND OBJECTIVES: Puberty onset and development contribute substantially to adolescents' bone mass and body composition. Our objective with this study was to examine the effects of gonadotropin-releasing hormone agonists (GnRHa) on these puberty-induced changes among youth with gender dysphoria (GD).

METHODS: Medical records of the endocrine diversity clinic in an academic children's hospital were reviewed for youth with GD seen from January 2006 to April 2017 with at least 1 baseline dual-energy radiograph absorptiometry measurement.

RESULTS: At baseline, transgender females had lower lumbar spine (LS) and left total hip (LTH) areal bone mineral density (aBMD) and LS bone mineral apparent density (BMAD) *z* scores. Only 44.7% of transgender youth were vitamin D sufficient. Baseline vitamin D status was associated with LS, LTH aBMD, and LS BMAD *z* scores. Post-GnRHa assessments revealed a significant drop in LS and LTH aBMD *z* scores (transgender males and transgender females) without fractures and LS BMAD (transgender males), an increase in gynoid (fat percentage), and android (fat percentage) (transgender males and transgender females), and no changes in BMI *z* score.

CONCLUSIONS: GnRHa monotherapy negatively affected bone mineral density of youth with GD without evidence of fractures or changes in BMI *z* score. Transgender youth body fat redistribution (android versus gynoid) were in keeping with their affirmed gender. The majority of transgender youth had vitamin D insufficiency or deficiency with baseline status associated with bone mineral density. Vitamin D supplementation should be considered for all youth with GD.

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Dr Navabi conceptualized and designed the study, collected data, conducted initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Tang conducted the analyses and reviewed and revised the manuscript; Dr Khatchadourian reviewed and revised the manuscript; Dr Lawson conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Despite short-term efficacy and safety of gonadotropin-releasing hormone agonist (GnRHa) to suppress puberty in youth with gender dysphoria, evidence on the potential impacts of GnRHa monotherapy on bone mass accrual and body composition and the role of vitamin D status is limited.

WHAT THIS STUDY ADDS: GnRHa monotherapy for gender dysphoria negatively affected bone mineral density without changes in BMI *z* score. Transgender youth fat redistribution (android/gynoid) and transgender females lean body mass and total body fat changes were in keeping with their affirmed gender. Most transgender youth had low vitamin D levels at baseline.

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The number of youth with gender dysphoria (GD) seeking gender-affirming care has increased significantly.[1–4] Endocrine Society[5] and World Professional Association for Transgender Health[6] guidelines recommend gonadotropin-releasing hormone agonists (GnRHas) for puberty suppression in youth with GD who are in Tanner stages 2 to 5. Efficacy and safety of GnRHa to arrest pubertal development in central precocious puberty is well described[7] with short-term efficacy and safety of GnRHa in youth with GD.[8,9] However, there are concerns about puberty suppression effects on bone mass accrual of youth with GD[5,8–11] because sex steroids are fundamental for bone acquisition during puberty and maintenance of bone mass in adulthood.[12,13] In small studies, researchers have found that GnRHa in youth with GD are associated with decreased bone mineral density (BMD) *z* scores and bone turnover markers.[11,14–17] Periodic monitoring of BMD by dual-energy radiograph absorptiometry (DXA) in youth with GD is currently recommended by the Endocrine Society[5] and International Society for Clinical Densitometry.[18] The scarcity of evidence on effects of GnRHa on bone health and body composition of youth with GD motivated us to retrospectively review all youth with GD managed at the endocrine diversity clinic of the Children's Hospital of Eastern Ontario (CHEO). In addition, we aimed to characterize vitamin D status of youth with GD and its relationship with bone health, as well as assess efficacy of supplemental vitamin D with 1000 to 2000 IU daily.

METHODS

Study Subjects

Medical records of the 198 youth <18 years of age seen at the endocrine diversity clinic at CHEO from January 2006 to April 2017 were retrospectively reviewed, and the 172 youth (86.9%) with at least 1 DXA measurement were included in this study. To allow a minimum follow-up time of 18 months, the study population's medical records were last reviewed in January 2019. GD diagnosis was based on adolescent medicine specialist assessments, which typically preceded the referral to the endocrine diversity clinic.

CHEO Endocrine Diversity Clinic Management of Youth With GD

Our center uses the GnRHa formulation of leuprolide acetate, historically starting with 3 doses of 7.5 mg intramuscularly every 4 weeks, followed by 11.25 mg intramuscularly every 12 weeks after confirmation of puberty suppression clinically and biochemically. GD management includes areal bone mineral density (aBMD) measurements by DXA with Lunar Prodigy system, and aBMD *z* scores are determined on the basis of birth-assigned sex, age, and ethnicity. Lumbar spine (LS) (L2–L4) and left total hip (LTH) aBMD *z* scores are usually assessed at baseline and every 12 months; however, youth with an aBMD *z* score below 2 SDs or significant drop (≥ 1 SD) in LS aBMD *z* score undergo BMD every 6 months and a lateral spine radiograph for vertebral fracture assessment. Youth with poor calcium intake are advised to take calcium carbonate 500 mg twice daily to meet the Institute of Medicine's[19] recommended dietary allowance. All youth are advised to take vitamin D 1000 to 2000 IU daily. Serum 25-hydroxyvitamin D (25OHD) levels are assessed at baseline and monitored every 6 to 12 months. Vitamin D status is classified on the basis of 25OHD level, with <30 nmol/L indicating deficiency, 30 to 50 nmol/L indicating insufficiency, and >50 nmol/L indicating sufficiency.[20]

Given the retrospective nature of the study and variable timing of baseline and follow-up DXA results relative to GnRHa initiation, pre-GnRHa DXA was defined as DXA scan within "−180 to +30" days of GnRHa initiation. Post-GnRHa DXA was defined as DXA scan at "≥ +180" days of GnRHa initiation, as long as this assessment was completed within 90 days of gender-affirming hormone initiation or GnRHa discontinuation.

Measurements

Birth-assigned sex, affirmed gender, Tanner stage at initial assessment, and anthropometrics (height and weight) at baseline and follow-up visits were retrieved from medical records. BMI *z* score was calculated on the basis of 2014 revised World Health Organization growth charts for Canada.[21]

Pre- and post-GnRHa DXA results were used to retrieve aBMD (grams per square centimeters) of LS, LTH, and total body less head (TBLH). Volumetric BMD was calculated as bone mineral apparent density (BMAD) (grams per cubic centimeters) at LS by using the method of Kroger et al[22] as "LS aBMD × [4/(π × width)]." LS BMAD *z* score was calculated on the basis of available reference for age-matched birth-assigned gender BMAD mean and SD.[23]

DXA is the most readily available and valid method of 3 compartmental body analyses.[24] In this study, we used pre- and post-GnRHa DXA results to extract the following variables: lean body mass (LBM) (kilograms), total body fat (TBF) (percentage), TBF (kilograms), regional fat mass ratios (ie, trunk/total, legs/total, and extremities/total), fat distribution in the form of android (fat percentage)

and gynoid (fat percentage), as well as bone mineral content (BMC) (kilograms) and BMC *z* score. TBF (percentage) *z* score was calculated on the basis of age-matched birth-assigned sex TBF (percentage), with mean and SD as "logarithm natural (Ln) TBF (%) – (Ln TBF (%) mean/ Ln TBF (%) SD)" for transgender females and Ln "(TBF (%) +10) – (Ln TBF (%) mean/Ln TBF (%) SD)" for transgender males.[23] LBM *z* score was calculated on the basis of age-matched birth-assigned sex LBM mean and SD.[23]

Statistical Analysis

Normally distributed data were expressed as mean ± SD and compared with the paired sample *t* test. Data that were not normally distributed were expressed as median and interquartile range and the Wilcoxon rank test used for comparison. $P < .05$ was considered statistically significant. However, bond percolation threshold was also used to determine statistical significance, corrected for multiple testing.

RESULTS

The study included 172 youth with GD; 119 (69.2%) youth self-identified as transgender males (age 15.2 ± 1.8 [SD] years; 90.7% Tanner 4–5), 51 (29.7%) youth as transgender females (age 15.4 ± 2.0 years; 80.3% Tanner 4–5), and 2 (1.1%) youth as nonbinary. Baseline body composition and BMD profiles are summarized in Table 1; transgender females had lower *z* scores at LS aBMD, LS BMAD, LTH aBMD, and BMC than transgender males.

At baseline, the majority (55.2%) of transgender youth were found to have vitamin D deficiency or insufficiency (Table 2). Baseline vitamin D status was associated with baseline LS aBMD, LS BMAD, and LTH *z* scores (Fig 1). Supplementation with 1000 to 2000 IU of vitamin D daily improved the vitamin D status with no case of vitamin D toxicity (Table 2).

A subgroup of the study population, namely, 36 (30.5%) transgender females and 80 (67.8%) transgender males with pre- and post-GnRHa DXA, was analyzed for GnRHa-associated changes. Pre-GnRHa DXA was done −51.4 ± 41.3 days (range −158 to +28 days) relative to GnRHa initiation; post-GnRHa DXA was done 355.2 ± 96.7 days or median of 352.5 (294.5, 385.8) days (range 188–676 days) after GnRHa initiation. The mean time interval between pre- and post-DXA scans was 406.7 ± 98.3 days (range 210–720 days).

BMD profiles and body composition after GnRHa as well as corresponding changes relative to baseline characteristics are summarized in Table 3. LS, LTH, and TBLH aBMD *z* scores dropped significantly among both transgender males and transgender females, whereas LS BMAD *z* scores decreased significantly among transgender males. Considering the limited number of transgender youth at early stages of puberty,[2,3] no statistical comparison of subgroups based on puberty status was done.

Four transgender youth (one birth-assigned girl and 3 birth-assigned males) had a baseline LS aBMD *z* score below 2 SDs, with 20 transgender youth (all transgender males) having >1-SD drop (1.37 ± 0.26) in their follow-up LS aBMD *z* score. Each of these youth had a subsequent lateral spine radiograph, none of which revealed a vertebral fracture.

Transgender males' post-GnRHa body composition analysis revealed significant increases in BMI, LBM (kilograms), TBF (percentage), android (fat percentage), and gynoid (fat percentage); there was no significant change in BMI *z* score, LBM *z* score, or TBF (%) *z* score. Transgender females showed a significant increase in TBF (percentage), TBF (percentage) *z* score, and gynoid (fat percentage), as well as a drop in LBM *z* score. GnRHa-associated changes in body compartment *z* scores and BMI *z* score were not different between transgender youth with baseline BMI percentiles above and below the obesity risk (85%) cutoff percentile (Table 4).

DISCUSSION

With this study, we reviewed BMD and body composition changes in youth with GD after 355.2 ± 96.7 days of GnRHa monotherapy. Youth identifying as transgender males constituted 69.2% of study population in keeping with the current trend of overrepresentation (50%–90%) of birth-assigned female patients in GD clinics.[3,25,26]

Baseline BMD characteristics were remarkable for transgender females' lower LS aBMD and BMAD *z* scores compared with those of transgender males. Similar baseline differences were previously observed in studies among youth[11,14,15,17] and adult[27] transgender females. Klink et al[15] suggested that lower engagement in physical activities, as is typical for transgender females, is a factor, as well as pubertal stage. Despite lack of consistent records of physical activity among our study population, literature supports reduced involvement of sexual minorities in moderate to vigorous physical activities and team sports.[28] We believe it is prudent to consider evaluating physical activity level as part of baseline and follow-up assessments of youth with GD, although lack of objective scales or specific recommendations from the Endocrine Society or World Professional Association for

TABLE 1 Baseline Body Composition and BMD Profiles at LS and LTH

	Transgender Males (n = 119)		Transgender Females (n = 51)		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	P[a]
LS					
aBMD, g/cm^2	1.13 (0.17)	1.16 (1.04 to 1.25)	0.98 (0.18)	0.968 (0.84 to 1.13)	<.001
aBMD z score	0.04 (1.10)	0.1 (−0.70 to 0.70)	−0.84 (1.29)	−0.9 (−1.8 to 0.00)	<.001
BMAD, g/cm^3	0.37 (0.46)	0.38 (0.33 to 0.41)	0.31 (0.04)	0.31 (0.29 to 0.34)	<.001
BMAD z score	−0.10 (1.00)	0.01 (−0.88 to 0.64)	−0.22 (1.41)	−0.08 (−0.99 to 0.64)	<.001
LTH					
aBMD, g/cm^2	1.00 (0.15)	1.02 (0.90 to 1.11)	0.95 (0.16)	0.94 (0.813 to 1.10)	NS
aBMD z score	0.10 (1.06)	0.2 (−0.70 to 0.90)	−0.44 (1.39)	−0.5 (−1.60 to 0.30)	<.001
BMC, kg	2.40 (0.54)	2.40 (2.00 to 2.74)	2.39 (0.65)	2.27 (1.96 to 2.83)	NS
BMC z score	0.05 (1.30)	0.05 (−0.86 to 0.93)	−0.66 (1.35)	−0.91 (−1.58 to 0.13)	.001
LBM, kg	36.24 (56.14)	36.46 (32.81 to 39.75)	45.74 (9.98)	44.66 (39.27 to 53.55)	.005
LBM z score	−1.03 (1.22)	−1.15 (−1.86 to −0.34)	−1.19 (1.45)	−1.41 (−2.4 to −0.24)	NS
TBF, %	37.14 (10.46)	37 (29.10 to 45.80)	24.45 (12.48)	24.2 (14.60 to 37)	<.001
TBF z score, %	1.68 (0.96)	1.76 (1.04 to 2.44)	1.42 (1.02)	1.58 (0.62 to 2.38)	NS
BMI	24.04 (5.17)	22.99 (20.04 to 27.66)	23.22 (6.33)	20.38 (18.30 to 26.61)	NS
BMI z score	0.89 (1.25)	0.86 (0.07 to 1.85)	0.62 (1.67)	0.72 (−0.67 to 2.04)	NS

NS, nonsignificant.
[a] t test.

Transgender Health[5,6] are challenges in clinical practice.

Baseline body composition comparison of transgender males and transgender females was remarkable for lower BMC z score among transgender females and no difference in LBM and TBF (percentage) z scores. Of note, both transgender males and transgender females had higher baseline TBF and lower baseline LBM relative to the birth-assigned sex population; however, only transgender females had a lower baseline BMC z score. The latter is likely secondary to factors like physical activity, LBM, and BMI rather than delayed bone accrual, and the noted higher TBF among transgender females may have contributed to it, as some evidence suggests that higher body fat attenuates bone density in males while supporting bone density in females.[29]

At baseline, the majority (55.2%) of transgender youth had vitamin D deficiency or insufficiency with vitamin D status associated with BMD at LS and LTH. Some evidence suggests potential bone protective effects of physical activity in the presence of very low serum 25OHD.[30] However, the conceivably lower physical activity in transgender youth may heighten vitamin D deficiency effects on BMD. In addition, the combination of low vitamin D and low calcium intake (<600 mg/day) may impair LS mineralization in postmenarchal females.[31] These all suggest that vitamin D and calcium supplementation should be considered for all youth with GD regardless of whether they are considering puberty suppression.

TABLE 2 Vitamin D Status Among Youth With GD

		Vitamin D Status, n (%)		
	n	Deficiency[a]	Insufficiency[b]	Sufficiency[c]
Baseline	170	30 (17.6)	64 (37.6)	76 (44.6)
First follow-up	146	5 (3.4)	26 (17.8)	115 (78.8)
Second follow-up	110	4 (3.6)	19 (17.3)	87 (79.1)
Third follow-up	63	1 (1.6)	7 (11.1)	55 (87.3)

[a] 25OHD <30 nmol/L.
[b] 25OHD 30 to 50 nmol/L.
[c] 25OHD >50 to 250 nmol/L.

GnRHa monotherapy negatively affected transgender youth aBMD z scores at LS, LTH, and TBLH levels and transgender males' LS BMAD z scores. The most pronounced decrease in z score (>0.5) was noted in transgender males' LS aBMD and BMAD. The majority of the youth were late pubertal; this observed decrease is in line with other studies[11,14] and explained by the significant decrease of estrogen on the trabecular rich bone at the spine. Transgender males at early stages of puberty seemed to have less pronounced LS aBMD z score changes. Schagen et al[11] found that transgender youth in both early and late stages of puberty had a drop in aBMD z scores after 24 months of GnRHa regardless of puberty status, but this was more pronounced in transgender males in late puberty, assessing BMD z scores on the basis of sex assigned at birth. Similarly, because we were assessing the effect of GnRHa monotherapy, BMD z scores were based on sex assigned at birth. In future studies, researchers should consider

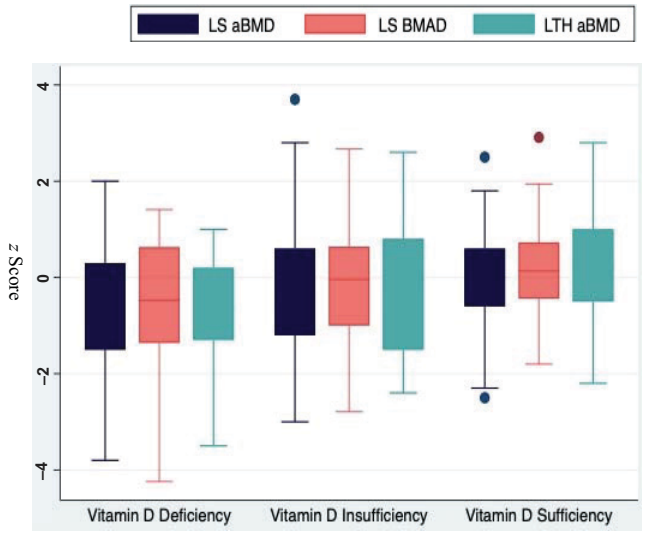

FIGURE 1
Pre-GnRHa BMD profiles and baseline vitamin D status.

whether to use sex assigned at birth or identified gender when assessing the effect of gender-affirming hormones on bone health in transgender youth. Given the limited evidence on transgender youth in early puberty, the degree of BMD changes after puberty suppression in early puberty is not known. This is an important clinical concern for transgender youth in early stages of puberty who are treated with a longer course of GnRHa therapy before gender-affirming hormones are considered.[5,6]

Current evidence on GnRHa effects on body composition of youth with GD suggests a stable or slightly increased BMI *z* score, as well as an increase in fat percentage and drop in LBM.[8,15,16,32] In our study, GnRHa was not associated with any significant changes in BMI *z* score. Among transgender females, GnRHa was associated with a significant increase in TBF (percentage) *z* score and drop in LBM *z* score. If transgender females were on GnRHa longer, a significant change in BMI and TBF (percentage) *z* scores could occur because of loss of testosterone effects on LBM and TBF[33,34] at advanced stages of puberty. The observed fat redistribution (android versus gynoid) is in keeping with youth affirmed gender's typical fat distribution.[33–35]

Clinical Implications

Evidence on GnRHa-associated changes in body composition and BMD will help health care professionals involved in the care of youth with GD to counsel appropriately and optimize their bone health. Given the absence of vertebral fractures detected in those

TABLE 3 Body Composition Analysis and BMD Profile of Youth With GD After GnRHa

	Transgender Males (n = 80)			Transgender Females (n = 36)		
	Post-GnRHa Mean (SD)	Δ Post-Pre Mean (95% CI)	P,[a] SS[b]	Post-GnRHa Mean (SD)	Δ Post-Pre Mean (95% CI)	P, SS
BMD changes						
LS aBMD *z* score	−0.72 (0.97)	−0.74 (−0.85 to −0.63)	<.001 S	−1.33 (1.39)	−0.33 (−0.46 to −0.19)	<.001 S
LS BMAD *z* score	−0.76 (0.93)	−0.59 (−0.74 to −0.45)	<.001 S	−0.76 (1.48)	−0.37 (−0.61 to −0.14)	.003 NS
LTH aBMD *z* score	−0.31 (0.99)	−0.33 (−0.40 to −0.26)	<.001 S	−1.03 (1.64)	−0.46 (−0.60 to −0.31)	<.001 S
TBLH aBMD *z* score	0.03 (1.05)	−0.34 (−0.43 to −0.25)	<.001 S	−0.48 (1.49)	−0.34 (−0.48 to −0.21)	<.001 S
Body composition changes						
BMI	25.12 (6.04)	1.36 (0.75 to 1.97)	<.001 S	23.18 (6.64)	0.57 (−0.46 to 1.60)	.120
BMI *z* score	0.99 (1.30)	0.15 (0.01 to 0.29)	.083	0.45 (1.69)	−0.10 (−0.38 to 0.17)	.475
TT-FMR	0.49 (0.04)	0.00 (−0.01 to 0.01)	1.0	0.48 (0.05)	−0.02 (−0.03 to 0.00)	.010 NS
LT-FMR	0.38 (0.04)	0.00 (−0.01 to 0.00)	.209	0.39 (0.04)	0.01 (0.00 to 0.02)	.013 NS
ET-FMR	0.97 (0.17)	0.00 (−0.02 to 0.02)	.813	1.03 (0.19)	0.08 (0.02 to 0.13)	.004 NS
Android, fat %	42.21 (12.36)	2.75 (1.21 to 4.28)	<.001 S	33.41 (13.97)	4.18 (1.09 to 7.28)	.002 NS
Gynoid, fat %	46.76 (7.81)	1.83 (0.77 to 2.88)	<.001 S	38.70 (9.30)	7.17 (4.64 to 9.69)	<.001 S
TBF, kg	25.00 (12.48)	2.19 (0.75 to 3.63)	.001 S	20.44 (13.57)	4.41 (2.22 to 6.60)	<.001 S
TBF, %	39.93 (10.03)	2.21 (0.99 to 3.43)	<.001 S	31.14 (11.62)	5.36 (2.83 to 7.88)	<.001 S
TBF, *z* score, %	1.78 (0.90)	0.13 (0.00 to 0.25)	.053	2.46 (0.51)	1.05 (0.79 to 1.32)	<.001 S
LBM, kg	37.45 (5.55)	1.05 (0.45 to 1.64)	<.001 S	43.17 (7.86)	−1.58 (−3.0 to −0.15)	.006 NS
LBM *z* score	−1.01 (1.28)	−0.02 (−0.16 to 0.12)	.891	−1.99 (1.58)	−0.73 (−0.95 to −0.5)	<.001 S
BMC, kg	2.37 (0.43)	0.006 (−0.03 to 0.04)	.998	2.40 (0.46)	0.15 (0.10 to 0.20)	<.001 S
BMC *z* score	−0.39 (1.12)	−0.39 (−0.51 to −0.28)	<.001 S	−0.99 (1.18)	−0.12 (−0.26 to 0.02)	.059

ET-FMR, extremities/trunk fat mass ratio; LT-FMR, legs/total fat mass ratio; NS, not significant; S, statistically significant; TT-FMR, trunk/total fat mass ratio.
[a] Wilcoxon rank test.
[b] Statistical significance of .0011 to correct for multiple testing.

TABLE 4 GnRHa-Induced Body Compartment and BMI Changes Among Transgender Youth Subdivided by Baseline BMI Percentile at Cutoff for Obesity Risk

	BMI ≤85 Percentile		BMI >85 Percentile			
	n	Mean (SD)	*n*	Mean (SD)	Difference (95% CI)	*P*[a] Value, SS[b]
Δ BMI *z* score	71	0.11 (0.62)	47	0.00 (0.79)	0.11 (−0.14 to 0.37)	0.867, NS
Δ TBF *z* score, %	71	0.58 (0.91)	47	0.19 (0.44)	0.39 (0.11 to 0.67)	0.050, NS
Δ LBM *z* score	71	−0.31 (0.66)	47	−0.15 (0.81)	−0.15 (−0.42 to 0.11)	0.292, NS
Δ BMC *z* score	71	−0.26 (0.49)	47	−0.37 (0.49)	0.11 (−0.07 to 0.30)	0.326, NS

NS, nonsignificant.
[a] Wilcoxon rank test.
[b] Statistical significance of .01 to correct for multiple testing.

with significant decreases in their LS *z* scores, the significance of BMD effects of GnRHa in transgender youth needs further study, as well as whether future spine radiographs are needed on the basis of BMD trajectory. This study can advance clinical practice guidelines and research in the field.

Strengths and Limitations

The study strengths include the large study population with baseline assessments and pre-post GnRHa subgroup analysis. This is the first study used to examine vitamin D status and provide a comprehensive assessment of body composition after GnRHa monotherapy. Lack of consistent records of physical activity at baseline and follow-up visits limited analysis of physical activity's role as a potential contributing factor to bone health and body composition. The small sample size of youth in early puberty prevented comparison of GnRHa effects in early versus late puberty.

CONCLUSIONS

BMI *z* score does not appear to increase significantly in transgender youth on GnRHa monotherapy; however, it is associated with an increase in TBF (percentage) *z* score and reduction in LBM *z* score of transgender females. Transgender youth body fat redistribution (android versus gynoid) after GnRHa and transgender females' body composition changes after GnRHa were in keeping with youth affirmed gender. GnRHa monotherapy in transgender youth is associated with a decrease in LS, LTH, and TBLH aBMD *z* scores. Vitamin D sufficiency was uncommon among transgender youth. Vitamin D and calcium supplementation should be considered for all youth with GD, particularly those who seek pubertal suppression. Given the negative effects of GnRHa monotherapy on BMD, bone density and 25OHD should be considered at baseline and follow-up care of adolescents with GD on GnRHa monotherapy.

ABBREVIATIONS

aBMD: areal bone mineral density
BMAD: bone mineral apparent density
BMC: bone mineral content
BMD: bone mineral density
CHEO: Children's Hospital of Eastern Ontario
DXA: dual-energy radiograph absorptiometry
GD: gender dysphoria
GnRHa: gonadotropin-releasing hormone agonist
LBM: lean body mass
Ln: logarithm natural
LS: lumbar spine
LTH: left total hip
TBF: total body fat
TBLH: total body less head
25OHD: 25-hydroxyvitamin D

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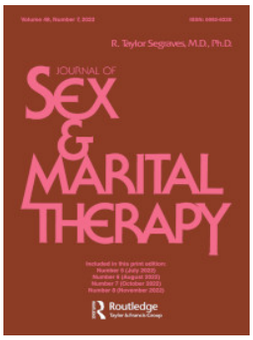

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Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults

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REVIEW

Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults

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ABSTRACT

In less than a decade, the western world has witnessed an unprecedented rise in the numbers of children and adolescents seeking gender transition. Despite the precedent of years of gender-affirmative care, the social, medical and surgical interventions are still based on very low-quality evidence. The many risks of these interventions, including medicalizing a temporary adolescent identity, have come into a clearer focus through an awareness of detransitioners. The risks of gender-affirmative care are ethically managed through a properly conducted informed consent process. Its elements—deliberate sharing of the hoped-for benefits, known risks and long-term outcomes, and alternative treatments—must be delivered in a manner that promotes comprehension. The process is limited by: erroneous professional assumptions; poor quality of the initial evaluations; and inaccurate and incomplete information shared with patients and their parents. We discuss data on suicide and present the limitations of the Dutch studies that have been the basis for interventions. Beliefs about gender-affirmative care need to be separated from the established facts. A proper informed consent process can both prepare parents and patients for the difficult choices that they must make and can ease professionals' ethical tensions. Even when properly accomplished, however, some clinical circumstances exist that remain quite uncertain.

KEYWORDS

Informed consent; ethics; gender dysphoria; gender identity; detransition

Introduction

Reconsideration of the meanings, purposes, indications, and processes of informed consent for transgender-identified youth is urgently needed. Parents of gender atypical children are considering social transition as early as preschool or grade school. Parents of preteens and teens are considering supporting their children's wishes to present in a new gender, take puberty blockers and cross-sex hormones, and plan for surgical alterations. College-aged youth are declaring new identities for the first time and obtaining hormones and surgery without their parents' knowledge.

When uncertain parents of children and teens consult their primary care providers, they are usually referred to specialty gender services. Parents and referring clinicians assume that specialists with "gender expertise" will undertake a thorough evaluation. However, the evaluations preceding the recommendation for gender transition are often surprisingly brief (Anderson & Edwards-Leeper, 2021) and typically lead to a recommendation for hormones and surgery, known as *gender-affirmative* treatment.

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Despite the widely recognized deficiencies in the evidence supporting gender-affirmative interventions (National Institute for Health & Care Excellence, 2020a; 2020b), the process of obtaining informed consent from patients and their families has no established standard. There is no consensus about the requisite elements of evaluations, nor is there unanimity about how informed consent processes should be conducted (Byne et al., 2012). These two matters are inconsistent from practitioner to practitioner, clinic to clinic, and country to country.

Social transition, hormonal interventions, and surgery have profound implications for the course of the lives of young patients and their families. It is incumbent upon professionals that these consequences be thoroughly, patiently clarified over time prior to undertaking any element of transition. The informed consent process does not preclude transition; it merely educates the family about the state of the science underpinning the decision to transition. Social transition, hormones, and surgeries are unproven in a strict scientific sense, and as such, to be ethical, require a thorough and fully informed consent process.

Ethical Concerns About Inadequate Informed Consent

The concept of informed consent in medicine has roots in both ethical theory and law. The ethical foundation is centered in the principles of beneficence, justice, and respect for autonomy, while the legal issues have to do with questions of malpractice (Katz et al., 2016).

Patients consenting to treatment must meet age-based and decisional capacity requirements (Katz et al., 2016). Minors less than the age of consent participate in decision-making by providing *assent*—an agreement with the intervention. The limited maturational cognitive capacities of minors are the key reason why parents serve as the ethical and legal surrogates for medical decision-making, tasked with signing an informed consent document (Grootens-Wiegers, Hein, van den Broek, & de Vries, 2017).

The informed consent process consists of three main elements: a disclosure of information about the nature of the condition and the proposed treatment and its alternatives; an assessment of patient and caregiver understanding of the information and capacity for medical decision-making; and obtaining the signatures that signify informed consent has been obtained (Katz et al., 2016). The current expectation that clinicians and institutions are required to thoroughly inform their patients about the benefits, risks, and uncertainties of a particular treatment, as well as about alternatives, has a long legal history in the United States (Lynch, Joffe, & Feldman, 2018).

Ethical concerns about inadequate informed consent for trans-identified youth have several potentially problematic sources, including *erroneous assumptions* held by professionals; *poor quality of the evaluation process*; and *incomplete and inaccurate information* that the patients and family members are given.

These concerns are amplified by the *dramatic growth* in demand for youth gender transition witnessed in the last several years that has led to a perfunctory informed consent process. A rushed process does not allow for a proper discussion of not only the benefits, but the profound risks and uncertainties associated with gender transition, especially when gender transition is undertaken before mature adulthood.

a. *Dramatic growth in demand for services threatens true informed consent*

Gender identity variations were thought to be extremely rare a generation ago. While the incidence in youth had not been officially estimated, in adults it was 2-14 per 100,000 (American Psychiatric Association, 2013, p. 454). However, around 2006, the incidence among youth began to rise, with a dramatic increase observed in 2015 (Aitken et al., 2015, de Graaf, Giovanardi, Zitz, & Carmichael, 2018). Currently, 2-9% of U.S. high school students identify as transgender, while in colleges, 3% of males and 5% of females identify as gender-diverse (American College Health Association, 2021; Johns et al., 2019; Kidd et al., 2021).

Whereas previously most of the affected individuals identified as the opposite sex, there is now a growing trend toward identifying as *nonbinary*: neither male nor female or both male and female (Chew et al., 2020). A recent study reported that the majority of transgender-identifying youth (63%) now have a non-binary identity (Green, DeChants, Price, & Davis, 2021). Although the incidence of natal males asserting a trans identity in adolescence has significantly increased, the dramatic increase is driven primarily by the natal females requesting services (Zucker, 2017). Many suffer from significant comorbid mental health disorders, have neurocognitive difficulties such as ADHD or autism or have a history of trauma (Becerra-Culqui et al., 2018; Kozlowska, McClure, et al., 2021).

The increase in rates of transgender identification is reflected in the numbers of youth seeking help from medical professionals. For example, according to data reported by the Tavistock gender clinic in the UK, in 2009, there were 51 requests for services (de Graaf et al., 2018); in 2019-2020, 2728 referrals were recorded—a 53-fold increase in just over a decade (Tavistock & Portman NHS Foundation Trust, 2020). The growing number of urban transgender health centers that have arisen in recent years (HRC, n.d.) reflects the increased demand for gender-related medical care among young people in North America Australia, and Europe.

This unprecedented increase has created pressure on institutions and practitioners to rapidly evaluate these youth and make recommendations about treatment. To respond to growing demand, an innovative *informed consent model of care* has been developed. Under this model, mental health evaluations are not required, and hormones can be provided after just one visit following the collection of a patient's or guardian's consent signature (Schulz, 2018). The provision of transition services under this model of care is available not just to those over 18, but for younger patients as well (Planned Parenthood League of Massachusetts, n.d.).

Although following the informed consent model of care for hormones and surgeries for youth may diminish clinicians' ethical or moral unease (Vrouenraets et al., 2020), we believe this model is the antithesis of true informed consent, as it jeopardizes the ethical foundation of patient autonomy. Autonomy is not respected when patients consenting to the treatment do not have an accurate understanding of the risks, benefits, and alternatives.

b. *Assumptions held by professionals influence the integrity of the informed consent process*

Gender-dysphoric children and teens can intensely occupy the belief that their lives will be immensely improved by transition. Clinicians who have embraced the gender-affirmative model of care operate on the assumption that children and teens know best what they need to be happy and productive (Ehrensaft, 2017). These professionals, responding to the youths' passionate pleas, see their role as validating the young person's fervent wishes for hormones and surgery and clearing the path for gender transition. In doing so, they privilege the ethical principle of respect for patient autonomy (Clark & Virani, 2021) over their obligations for beneficence and non-maleficence.

Many of the gender-affirmative clinicians subscribe to the theory of *minority stress* – the supposition that the frequently co-occurring psychiatric symptoms of gender-dysphoric individuals are a result of prejudice and discrimination brought about by gender non-conformity (Rood et al., 2016; Zucker, 2019), and that gender transition will ameliorate these symptoms. Some even claim that gender-affirmative care will successfully treat not only depression and anxiety but will also resolve neurocognitive deficits frequently present in gender-dysphoric individuals (Turban, 2018; Turban, King, Carswell, & Keuroghlian, 2020; Turban & van Schalkwyk, 2018). These latter assertions have proven controversial even among the proponents of gender-affirmative interventions (Strang et al., 2018; van der Miesen, Cohen-Kettenis, & de Vries, 2018). The minority stress theory as the sole explanatory mechanism for co-occurring mental health illness has also been questioned in light of the evidence that psychiatric symptoms frequently predate the onset of gender dysphoria (Bechard, VanderLaan, Wood, Wasserman, & Zucker, 2017; Kaltiala-Heino, Sumia, Työläjärvi, & Lindberg, 2015; Kozlowska, Chudleigh, McClure, Maguire,

& Ambler, 2021). Other clinicians recognize the limits of gender-affirmative care and are aware that youth with underlying psychiatric issues are likely to continue to struggle post-transition (Kaltiala, Heino, Työläjärvi, & Suomalainen, 2020), but, unaware of alternative approaches such as gender-exploratory psychotherapy or watchful waiting (Bonfatto & Crasnow, 2018; Churcher Clarke & Spiliadis, 2019; Spiliadis, 2019), these well-meaning professionals continue to treat youth with gender-affirmative interventions despite lingering doubts.

It is common for gender-affirmative specialists to erroneously believe that gender-affirmative interventions are a *standard of care* (Malone, D'Angelo, Beck, Mason, & Evans, 2021; Malone, Hruz, Mason, Beck, et al:, 2021). Despite the increasingly widespread professional beliefs in the safety and efficacy of pediatric gender transition, and the endorsement of this treatment pathway by a number of professional medical societies, the best available evidence suggests that the benefits of gender-affirmative interventions are of very low certainty (Clayton et al., 2021; National Institute for Health & Care Excellence, 2020a; 2020b) and must be carefully weighed against the health risks to fertility, bone, and cardiovascular health (Alzahrani et al., 2019; Biggs, 2021; Getahun et al., 2018; Hembree et al., 2017; Nota et al., 2019). Recently, emphasis has also been placed on psychosocial risks and as yet unknown medical risks (Malone, D'Angelo, et al., 2021).

Five scientific observations question and refute the assumption that an individual's experience of incongruence of sex and gender identity is best addressed by supporting the newly assumed gender identity with psychosocial and medical interventions.

1. The most foundational aspect of the diagnoses of "gender dysphoria" (DSM-5) and "gender incongruence" (ICD-11), requisite for the provision of medical treatment, is in flux, as professionals disagree on whether the presence of distress is a key diagnostic criterion, as stated in the DSM-5, or is irrelevant, as is the case according to the latest ICD-11 criteria (American Psychiatric Association, 2013; World Health Organization, 2019). Further, these diagnoses have never been properly field-tested (de Vries et al., 2021).
2. There are no randomized controlled studies demonstrating the superiority of various affirmative interventions compared to alternatives. There isn't even agreement about which outcome measures would be ideal in such studies.
3. There are few long-term follow-up studies of various interventions using predetermined outcome measures at designated intervals. Studies that have been conducted are, at best, inconsistent. Higher quality studies with longer-follow-up fail to demonstrate durable positive impacts on mental health (Bränström & Pachankis, 2020a; 2020b).
4. Rates of post-transition desistance, increased mental suffering, increased incidence of physical illness, educational failure, vocational inconstancy, and social isolation have not been established.
5. Numerous cross-sectional and prospective studies of transgender adults consistently demonstrate a high prevalence of serious mental health and social problems as well as suicide (Asscheman et al., 2011; Dhejne et al., 2011). Controversies about how to deal with trans-identified youth must consider the well described vulnerabilities of transgender adults.

It is equally important to realize that to date, research about alternative approaches, such as psychotherapy or watchful waiting, shares the scientific limitations of the research of more invasive interventions: there are no control groups, nor is there systematic follow-up at predetermined intervals with predetermined means of measurement (Bonfatto & Crasnow, 2018; Churcher Clarke & Spiliadis, 2019; Spiliadis, 2019). Parents and patients need to be informed of this as well.

Perhaps the single most problematic assumption held by some gender clinicians is that the young patients have simply been "born in the wrong body." This assumption seemingly frees clinicians from having to contend with the ethical dilemmas of recommending body-altering

interventions that are based on very low-quality evidence. Despite the principle of development that biology, psychosocial factors, and culture generate behavior, these clinicians may believe that atypical genders are created by biology. This reductionistic approach has been criticized repeatedly (Kendler, 2019).

While the origins of childhood or adolescent onset of gender incongruence have not yet been fully elucidated, brain studies of increasing technical sophistication have yet to demonstrate a distinct structure or pattern that accounts for an atypical gender identity, after statistically controlling for sexual orientation and exposure to exogenous hormones (Frigerio, Ballerini, & Valdés Hernández, 2021). Twin studies also demonstrate that while biology plays a role in one's experience of "gender incongruence," it is far from deterministic (Diamond, 2013).

A growing number of clinicians and researchers are noting that the dramatic rise of teens declaring a trans identity appears to be, at least in part, a result of peer influence (Anderson, 2022; Hutchinson, Midgen, & Spiliadis, 2020; Littman 2018; Littman, 2020; Zucker, 2019). Some have noted yet another influx of trans-identified youth emerging during the COVID lockdowns, and have hypothesized that increased isolation coupled with heavy internet exposure may be responsible (Anderson, 2022). While the research into the phenomenon of social influence as a contributor to trans identification of youth is still in its infancy, the possibility that clinicians are providing treatments with permanent consequences to address what may be transient identities in youth poses a serious ethical dilemma.

c. *Poor evaluations*

There is a growing recognition that rapid evaluations which disregard factors contributing to the development of gender dysphoria in youth are problematic. In November 2021, two-leaders of the World Professional Organization for Transgender Health (WPATH) warned the medical community that the "The mental health establishment is failing trans kids" (Anderson & Edwards-Leeper, 2021). Frequently, evaluations provided by gender clinicians may only ascertain the diagnosis of *gender dysphoria* (DSM-5) or its ICD-11 counterpart *gender incongruence*, and screen for conspicuous mental illness prior to recommending hormones and surgeries. These limited, abbreviated evaluations overlook, and as a result fail to address, the relevant issue of the forces that may have influenced the young person's current gender identity.

Confirming the young person's self-diagnosis of gender dysphoria or gender incongruence is easy. Clarifying the developmental forces that have influenced it and determining an appropriate intervention are not. Contextualizing these forces involves an understanding of child and adolescent developmental processes, childhood adversity, co-existing physical and cognitive disadvantages, unfortunate parental or family circumstances (Levine, 2021), as well as the role of social influence (Anderson, 2022; Anderson & Edwards-Leeper, 2021; Littman, 2018; 2021).

The poor quality of mental health evaluations has been a point of significant discontent for a growing number of parents of gender-dysphoric youth. Increasingly, parents have formed dozens of support groups in North America, Europe, Australia and New Zealand, united in their objections to the idea that the best or the only treatment for their gender-dysphoric children is affirmation (Genspect, 2021). These distressed parents, recognizing that their son or daughter may eventually decide to present to others as a trans person, want a psychotherapeutic investigation to understand what contributed to the development of this identity and an exploration of noninvasive treatment options. Frequently, they cannot find anyone in their community who does not recommend immediate affirmation.

The American Academy of Pediatrics' Committee of Bioethics recognizes that "parents…are better situated than others to understand the unique needs of their children and to make appropriate, caring decisions regarding their children's health care" (Katz et al., 2016). The plight of the families unable to find specialists capable of conducting thorough evaluations draws attention to the widespread acceptance of medical interventions for gender-dysphoric youth as the first line of treatment. The problem is that such care has been established through precedent rather

than through scientific demonstrations of its efficacy. We contend that parents and patients have a right to know this, and that it is the professionals' responsibility and obligation to inform them of the state of knowledge in this arena of care.

d. *Incorrect information shared*

In sharing the information with patients and families, two key areas of uncertainty must be emphasized. The first one is the uncertain permanence of a child's or an adolescent's gender identity (Littman, 2021; Ristori & Steensma, 2016; Singh, Bradley, & Zucker, 2021; Vandenbussche, 2021; Zucker, 2017). The second is the uncertain long-term physical and psychological health outcomes of gender transition (National Institute for Health & Care Excellence, 2020a; 2020b). Unfortunately, gender specialists are frequently unfamiliar with, or discount the significance of, the research in support of these two concepts. As a result, the informed consent process rarely adequately discloses this information to patients and their families.

Problematically, it is common for gender clinicians to emphasize the risk of suicide if a young person's wish to transition gender is not immediately fulfilled. There is a significant amount of misinformation surrounding the question of suicidality of trans-identified youth (Biggs, 2022). Providers of gender-affirmative care should be careful not to unwittingly propagate misinformation regarding suicide to parents and youths. They should also be reminded that any conversations about suicide should be handled with great care, due to its socially contagious nature (Bridge et al., 2020; HHS, 2021).

i. High rate of desistance/natural resolution of gender dysphoria in children is not disclosed

There have been eleven research studies to date indicating a high rate of resolution of gender incongruence in children by late adolescence or young adulthood without medical interventions (Cantor, 2020; Ristori & Steensma, 2016; Singh et al., 2021). An attempt has been made to discount the applicability of this research, suggesting that the studies were based on merely gender non-conforming, rather than truly gender-dysphoric, children (Temple Newhook et al., 2018). However, a reanalysis of the data prompted by this critique confirmed the initial finding: Among children meeting the diagnostic criteria for "Gender Identity Disorder" in DSM-IV (currently "Gender Dysphoria in DSM-5), 67% were no longer gender-dysphoric as adults; the rate of natural resolution for gender dysphoria was 93% for children whose gender dysphoria was significant but subthreshold for the DSM diagnosis (Zucker, et al., 2018). It should be noted that high resolution of childhood-onset gender dysphoria had been recorded before the practice of social transition of young children was endorsed by the American Academy of Pediatrics (Rafferty et al., 2018). It is possible that social transition will predispose a young person to persistence of transgender identity long-term (Zucker, 2020).

The information regarding the resolution of gender dysphoria among those with adolescent-onset gender dysphoria, which is currently the predominant presentation, is less clear. A growing body of evidence suggests that for many teens and young adults, a post-pubertal onset of transgender identification can be a transient phase of identity exploration, rather than a permanent identity, as evidenced by a growing number of young detransitioners (Entwistle, 2020; Littman, 2021; Vandenbussche, 2021). Previously, the rate of detransition and regret was reported to be very low, although these estimates suffered from significant limitations and were likely undercounting true regret (D'Angelo, 2018). However, in the last several years since gender-affirmative care has become popularized, the rate of detransition appears to be accelerating.

According to a recent study from a UK adult gender clinic, 6.9% of those treated with gender-affirmative interventions detransitioned within only 16 months of starting treatment, and another 3.4% had a pattern of care suggestive of detransition, yielding a rate of probable detransition in excess of 10%. Another 21.7% of patients disengaged from the clinic without completing

their treatment plan (Hall, Mitchell, & Sachdeva, 2021). While some of these individuals later reengaged with the gender service, the authors concluded, "detransitioning might be more frequent than previously reported." Another study from a UK primary care practice found that 12.2% of those who had started hormonal treatments either detransitioned or documented regret, while the total of 20% stopped the treatments for a wider range of reasons. The mean age of their presentation with gender dysphoria was 20, and the patients had been taking gender-affirming hormones for the average 5 years (17 months-10 years) prior to discontinuing.

Comparing these much higher rates of treatment discontinuation and detransition to the significantly lower rates reported by the older studies, the researchers noted: "Thus, the detransition rate found in this population is novel and questions may be raised about the phenomenon of overdiagnosis, overtreatment, or iatrogenic harm as found in other medical fields" (Boyd, Hackett, & Bewley, 2022 p.15). Indeed, given that regret may take up to 8-11 years to materialize (Dhejne, Öberg, Arver, & Landén, 2014; Wiepjes et al., 2018), many more detransitioners are likely to emerge in the coming years. Detransitioner research is still in its infancy, but two recently published studies examining detransitioner experiences report that detransitioners from the recently-transitioning cohorts feel they had been rushed to medical gender-affirmative interventions with irreversible effects, often without the benefit of appropriate, or in some instances any, psychologic exploration (Littman, 2021; Vandenbussche, 2021).

Clinicians should also disclose to patients and parents that there is no test which can accurately predict who will persist in their transgender identification upon reaching mature adulthood (Ristori & Steensma, 2016). Families should be made aware that a period of strong cross-sex identification in childhood is commonly associated with future homosexuality (Korte et al., 2008). Research in desistance confirms that the majority of youth whose gender dysphoria resolves naturally do indeed grow up to be gay, lesbian, or bisexual adults (Cantor, 2020, Appendix; Singh et al., 2021).

ii. Implications of very low-quality evidence that underlies the practice of pediatric gender transition are not explained

The evidence underlying the practice of pediatric gender transition is widely recognized to be of very low quality (Hembree et al., 2017). In 2020, the most comprehensive systematic review of evidence to date, commissioned by the UK National Health System (NHS) and conducted by the National Institute for Health and Care Excellence (NICE), concluded that the evidence for both puberty blocking and cross-sex hormones is of very low certainty (National Institute for Health & Care Excellence, 2020a; 2020b).

According to the NICE review of evidence for puberty blockers, the studies "are all small, uncontrolled observational studies, which are subject to bias and confounding, and are of very low certainty as assessed using modified GRADE [Grading of Recommendations, Assessment, Development and Evaluations]. All the included studies reported physical and mental health comorbidities and concomitant treatments very poorly" (National Institute for Health & Care Excellence, 2020a, p.13). NICE reached similar conclusions regarding the quality of the evidence for cross-sex hormones (National Institute for Health & Care Excellence, 2020b).

Problematically, the implications of administering a treatment with irreversible, life-changing consequences based on evidence that has an official designation of "very low certainty" according to modified GRADE is rarely discussed with the patients and the families. GRADE is the most widely adopted tool for grading the quality of evidence and for making treatment recommendations worldwide. GRADE has four levels of evidence, also known as certainty in evidence or quality of evidence: very low, low, moderate, and high (BMJ Best Practice, 2021). When evidence is assessed to be "very low certainty," there is a high likelihood that the patients will not experience the effects of the proposed interventions (Balshem et al., 2011).

In the context of providing puberty blockers and cross-sex hormones, the designation of "very low certainty" signals that the body of evidence asserting the benefits of these interventions is

highly unreliable. In contrast, several negative effects are quite certain. For example, puberty blockade followed by cross-sex hormones leads to infertility and sterility (Laidlaw, Van Meter, Hruz, Van Mol, & Malone, 2019). Surgeries to remove breasts or sex organs are irreversible. Other health risks, including risks to bone and cardiovascular health, are not fully understood and are uncertain, but the emerging evidence is alarming (Alzahrani et al., 2019; Biggs, 2021).

iii. The question of suicide is inappropriately handled

Suicide among trans-identified youth is significantly elevated compared to the general population of youth (Biggs, 2022; de Graaf et al., 2020). However, the "transition or die" narrative, whereby parents are told that their only choice is between a "live trans daughter or a dead son" (or vice-versa), is both factually inaccurate and ethically fraught. Disseminating such alarmist messages hurts the majority of trans-identified youth who are not at risk for suicide. It also hurts the minority who are at risk, and who, as a result of such misinformation, may forgo evidence-based suicide prevention interventions in the false hopes that transition will prevent suicide.

The notion that trans-identified youth are at alarmingly high risk of suicide usually stems from biased online samples that rely on self-report (D'Angelo et al., 2020; James et al., 2016; The Trevor Project, 2021), and frequently conflates suicidal thoughts and non-suicidal self-harm with serious suicide attempts and completed suicides. Until recently, little was known about the actual rate of suicide of trans-identified youth. However, a recent analysis of data from the biggest pediatric gender clinic in the world, the UK's Tavistock, found the rate of completed youth suicides to be 0.03% over a 10-year period, which translates into the annual rate of 13 per 100,000 (Biggs, 2022). While this rate is significantly elevated compared to the general population of teens, it is far from the epidemic of trans suicides portrayed by the media.

The "transition or die" narrative regards suicidal risk in trans-identified youth as a different phenomenon than suicidal risk among other youth. Making them an exception falsely promises the parents that immediate transition will remove the risk of suicidal self-harm. Trans patients themselves complain about the so-called "trans broken arm syndrome" – a frustrating pattern whereby physicians "blame" all the problems the patients are experiencing on their trans status, and a result, fail to perceive and respond to other sources of distress (Paine, 2021). Clinicians caring for trans-identified youth should be reminded that suicide risk in all patients is a multi-factorial phenomenon (Mars et al., 2019). To treat trans youths' suicidality as an exception is to deny them evidence-based care.

A recent study of three major youth clinics concluded that suicidality of trans-identifying teens is only somewhat elevated compared to that of youth referred for mental health issues unrelated to gender identity struggles (de Graaf et al., 2020). Another study found that transgender-identifying teens have relatively similar rates of suicidality compared to teens who are gay, lesbian and bisexual (Toomey, Syvertsen, & Shramko, 2018). Depression, eating disorders, autism spectrum conditions, and other mental health conditions commonly found in transgender-identifying youth (Kaltiala-Heino, Bergman, Työläjärvi, & Frisen, 2018; Kozlowska, McClure, et al., 2021; Morandini, Kelly, de Graaf, Carmichael, & Dar-Nimrod, 2021) are all known to independently contribute to the probability of suicide (Biggs, 2022; Simon & VonKorff, 1998; Smith, Zuromski, & Dodd, 2018).

The "transition or suicide" narrative falsely implies that transition will prevent suicides. Clinicians working with trans-identified youth should be aware that although in the short-term, gender-affirmative interventions can lead to improvements in some measures of suicidality (Kaltiala et al., 2020), neither hormones nor surgeries have been shown to reduce suicidality in the long-term (Bränström & Pachankis, 2020a; 2020b). Alarmingly, a longitudinal study from Sweden that covered more than a 30-year span found that adults who underwent surgical transition were 19 times more likely than their age-matched peers to die by suicide overall, with female-to-male participants' risk 40 times the expected rate (Dhejne et al., 2011, Table S1).

Another key longitudinal study from the Netherlands concluded that suicides occur at a similar rate at all stages of transition, from pretreatment assessment to post-transition follow-up (Wiepjes et al., 2020). The data from the Tavistock clinic also did not show a statistically significant difference between completed suicides in the "waitlist" vs. the "treated" groups (Biggs, 2022). Luckily, in both groups, completed suicides were rare events (which may have been responsible for the lack of statistical significance). Thus, we consider the "transition or die" narrative to be misinformed and ethically wrong.

In our experience working with trans-identified youth, an adolescent's suicidality can sometimes arise as a response to parental distress, resistance, skepticism, or wish to investigate the forces shaping the new gender identity before social transition and hormone therapy. When mental health professionals or other healthcare providers fail to recognize the legitimacy of parental concerns, or label the parents as transphobic, this only tends to intensify intrafamilial tension. Clinicians would be well-advised that gender transition is not an appropriate response to suicidal intent or threat, as it ignores the larger mental health and social context of the young patient's life—the entire family is often in crisis. Trans-identified adolescents should be screened for self-harm and suicidality, and if suicidal behaviors are present, an appropriate evidence-based suicide prevention plan should be put in place (de Graaf et al., 2020).

The Dutch Study: the questionable basis for the gender affirmative model of care for youth

Few practitioners of gender-affirmative interventions, and even fewer patients and families, realize that the foundation of the practice of medically transitioning minors stems from a single Dutch proof of concept study, the outcomes of which were documented in two publications (de Vries, Steensma, Doreleijers, Cohen, & Kettenis, 2011; de Vries et al., 2014). The former (de Vries et al., 2011) reported on cases who underwent puberty blockade, while the latter (de Vries et al., 2014) reported on a subset of the cases who completed surgeries.

The Dutch study subjects' high level of psychological functioning at 1.5 years after surgery, which was the study end point, was an impressive feat. However, both of the studies suffer from a high risk of bias due to their study design, which is effectively a non-randomized case series—one of the lowest levels of evidence (Mathes & Pieper, 2017; National Institute for Health & Care Excellence, 2020a). In addition, the studies suffer from limited applicability to the populations of adolescents presenting today (de Vries, 2020). The interventions described in the study are currently being applied to adolescents who were not cross-gender identified prior to puberty, who have significant mental health problems, as well as those who have non-binary identities—all of these presentations were explicitly disqualified from the Dutch protocol. Despite these limitations, the Dutch clinical experiment has become the basis for the practice of medical transition of minors worldwide and serves as the basis for the recommendations outlined in the 2017 Endocrine Society guidelines (Hembree et al., 2017).

We contend that the Dutch studies have been misunderstood and misrepresented as providing evidence of the safety and efficacy of these interventions for all youth. It is important that both the strengths and the weaknesses of these two studies are understood, as to date, the Dutch experience presents the best available evidence behind the practice of pediatric gender transition.

Rationale for pediatric transition

Prior to the 1990s, gender transitions were typically initiated in mature adults (Dhejne et al., 2011). However, it was noted that particularly for natal male patients, hormonal and surgical interventions failed to achieve satisfactory results, and patients had a "never disappearing masculine appearance" (Delemarre-van de Waal & Cohen-Kettenis, 2006). The lack of adequate cosmetic outcomes was thought to contribute to the frequently disappointing outcomes of medical

gender transition, with persistently high rates of mental illness and suicidality post-transition (Delemarre-van de Waal & Cohen-Kettenis, 2006; Dhejne et al., 2011; Ross & Need, 1989).

In the mid 1990s, a team of Dutch researchers hypothesized that by carefully selecting a subset of gender-dysphoric children who would likely be transgender-identified for the rest of their lives, and by medically intervening before puberty left an irreversible mark on their bodies, the cosmetic outcomes would be improved—and as a result, mental health outcomes might be improved (Gooren & Delemarre-van de Waal, 1996).

Mixed study findings

In 2014, the Dutch research team published a key longitudinal study of mental health outcomes of 55 youths who completed medical and surgical transition (de Vries et al., 2014). The 2014 paper (sometimes referred to as the "Dutch study") reported that for youth with severe gender dysphoria that started in early childhood and persisted into mid-adolescence, a sequence of puberty blockers, cross-sex hormones, and breast and genital surgeries (including a mandatory removal of the ovaries, uterus and testes), with ongoing extensive psychological support, was associated with positive mental health and overall function 1.5 years post-surgery.

While the Dutch reported resolution of gender dysphoria post-surgery in study subjects, the reported psychological improvements were quite modest (de Vries et al., 2014). Of the 30 psychological measurements reported, nearly half showed no statistically significant improvements, while the changes in the other half were marginally clinically significant at best (Malone, D'Angelo, et al., 2021). The scores in anxiety, depression, and anger did not improve. The change in the Children's Global Assessment Scale, which measures overall function, was one of the most impressive changes—however it too remained in the same range before and after treatment (de Vries et al., 2014).

Problematic discordance between reduced gender dysphoria and lack of meaningful improvements in psychological measures

The discordance between the marked reduction in gender dysphoria, as measured by the UGDS (Utrecht Gender Dysphoria Scale), and the lack of meaningful changes in psychological function using standard measures, warrants further examination. There are three plausible explanations for this lack of agreement. Any one of these three explanations calls into question the widely assumed notion that the medical interventions significantly improve mental health or lessen or eradicate gender dysphoria.

One possible explanation is that gender dysphoria as measured by UGDS, and psychological function as measured by most standard instruments, are not correlated. This contradicts the primary rationale for providing gender-affirmative treatments for youth (which is to improve psychological health and functioning), and if true, ethically threatens these medical interventions. The other plausible explanation stems from the high psychological function of all the subjects at baseline; the subjects were selected because they were free from significant mental health problems (de Vries et al., 2014). As a result, there was little opportunity to meaningfully improve. This explanation highlights a key limitation in applying the study's results to the majority of today's gender-dysphoric youth, who often present with a high burden of mental illness (Becerra-Culqui et al., 2018; Kozlowska, McClure, et al., 2021). The study cannot be used as evidence that these procedures have been proven to improve depression, anxiety, and suicidality.

A third possible explanation for the discordance between only minor changes in psychological outcomes but a significant drop in gender dysphoria comes from a close examination of the UGDS scale itself and how it was used by the Dutch researchers. This 12-item scale, designed by the Dutch to assess the severity of gender dysphoria and to identify candidates for hormones

and surgeries, consists of "male" (UGDS-aM) and "female" (UGDS-aF) versions (Iliadis et al., 2020). At baseline and after puberty suppression, biological females were given the "female" scale, while males were given the "male" scale. However, post-surgery, the scales were flipped: biological females were assessed using the "male" scale, while biological males were assessed on the "female" scale (de Vries et al., 2014). We maintain that this handling of the scales may have at best obscured, and at worst, severely compromised the ability to meaningfully track how gender dysphoria was affected throughout the treatment.

Consider this example. At baseline, a gender-dysphoric biological female would rate items from the "female" scale such as: "I prefer to behave like a boy" (item 1); "I feel unhappy because I have to behave like a girl" (item 6) and "I wish I had been born a boy" (item 12). Positive answers to these questions would have contributed to a high baseline gender dysphoria score. After the final surgery, however, this same patient would be asked to rate items from the "male" scale, including the following: "My life would be meaningless if I had to live as a boy" (item 1); "I hate myself because I am a boy" (item 6) and "It would be better not to live than to live as a boy" (item 12). A gender-dysphoric female would not endorse these statements (at any stage of the intervention), which would lead to a lower gender dysphoria score.

Thus, the detected drop in the gender dysphoria scores for biological males and females may have had less to do with the success of the interventions, and more to do with switching the scale from the "female" to the "male" version (and vice-versa) between the baseline and post-surgical period. This, too, may explain why no changes in gender dysphoria were noted between baseline and the puberty blockade phase, and were only recorded after the final surgery, when the scale was switched.

It must be considered that had the researchers administered the "flipped" scale earlier, at the completion of the puberty blocker stage, UGDS scale could have registered a reduction in gender dysphoria. Likewise, however, one must consider the possibility that had *both sets of scales* been administered to the same individual at baseline, a "reduction" in gender dysphoria could have been registered upon switching of the scale, *well before any interventions began*. The question here is whether the diminishment of quantitative measures of gender dysphoria is largely an artifact of what scale was used.

It must be noted that the UGDS measure has been demonstrated only to effectively differentiate between clinically referred gender-dysphoric individuals, non-clinically referred controls, and participants with disorders of sexual development, and was not designed to detect changes in gender dysphoria during treatment (Steensma, McGuire, Kreukels, et al. 2013). The presence of items such as "I dislike having erections" (item 11, UGDS-aM), which would have to be rated by birth-females, and "I hate menstruating because it makes me feel like a girl (item 10, UGDS-aF), which would be presented to birth-males, neither of which could be meaningfully rated by either at any stage of the interventions, further illustrates that UGDS has questionable validity for the purpose of detecting meaningful changes in gender dysphoria as a result of medical and surgical treatment.

The updated UGDS scale (UGDS-GS), developed by the Dutch after the publication of their seminal study, has eliminated the two-sex version of the scale in favor of a single battery of questions applicable to both sexes (McGuire et al., 2020). This change may lead to a more reliable measurement of treatment-associated changes in future research. Other gender dysphoria scales also exist (Hakeem, Črnčec, Asghari-Fard, Harte, & Eapen, 2016; Iliadis et al., 2020) and may or may not be better suited for the purposes of measuring the impact of medical interventions on underlying gender distress. Gender dysphoria, of course, may also prove to be a more complex concept than can be measured by any scale.

Other limitations

The two Dutch studies were conducted without a control group (de Vries et al., 2011; de Vires et al., 2014). Nor could the researchers control for mental health interventions, which all the

subjects received in addition to hormones and surgery. The Dutch only evaluated mental health outcomes and did not assess physical health effects of hormones and surgery. The sample size was small: the final study reported the outcomes of only 55 children, and as few as 32 were evaluated on key measures of psychological outcomes.

It is important to realize that the Dutch sample was carefully selected, which introduced a source of bias, and also challenges the study's applicability. From the 196 adolescents initially referred, 111 were considered eligible to start puberty blockers, and of this group, only the 70 most mature and mentally stable who proceeded to cross-sex hormones were included in the study (de Vries et al., 2011). Of note, 97% of the selected cases were attracted to members of their natal sex at baseline. All were cross-sex identified, with no cases of nonbinary identities. The final study only followed 55, rather than the original 70 cases, further excluding from reporting the outcomes of subjects who had experienced adverse events, including: one death from surgery-related complications and three cases of obesity and diabetes that rendered subjects ineligible for surgery. Three more subjects refused to be contacted or dropped out of care, which may mask adverse outcomes (de Vries et al., 2014).

There is no knowledge of the fate of 126 patients who did not participate in the Dutch study. Longer term outcomes of the subjects who did participate are lacking. We are aware of only one case of long-term follow-up for a female-to-male patient treated by the Dutch team in the 1990s. The case study describing the subject's functioning at the age of 33 found that the patient did not regret gender transition. However, he reported struggling with significant shame related to the appearance of his genitals and to his inability to sexually function; had problems maintaining long-term relationships; and experienced depressive symptoms (Cohen-Kettenis, Schagen, Steensma, de Vries, & Delemarre-van de Waal, 2011). Notably, these problems had not yet emerged when the same patient was assessed at the age of 20, when he reported high levels of satisfaction in general, and was "very satisfied with the results [of the metoidioplasty]" in particular (Cohen-Kettenis & van Goozen, 1998, p.248). Since the last round of psychological outcomes of the individuals in the Dutch study was obtained when the subjects were around 21 years of age (de Vries et al., 2014), it raises questions how they will fare during the decade when new developmental tasks, such as career development, forming long-term intimate relationships and friendships, or starting families come into focus.

As to the unknown outcomes of the patients rejected by the Dutch protocol, one study did report on 14 adolescents who sought gender reassignment in the same clinic, but were disqualified from treatment due to "psychological or environmental problems" (Smith, Van Goozen, & Cohen-Kettenis, 2001, p. 473). The study found that at follow-up 1-7 years after the original application, 11 of the 14 no longer wished to transition, and 2 others only slightly regretted not transitioning (Malone, D'Angelo, et al., 2021; Smith et al., 2001). This further underscores the importance of conducting research utilizing control groups and following the subjects for an extended period.

A recent attempt to replicate the results of the first Dutch study (de Vries et al., 2011) found no demonstrable psychological benefit from puberty blockade, but did find that the treatment adversely affected bone development (Carmichael et al., 2021). The final Dutch study (de Vries et al., 2014) has never been attempted to be replicated with or without a control group.

The scaling of the Dutch Protocol beyond original indications

The medical and surgical sequence of Dutch protocol has been aggressively scaled worldwide without the careful evaluations and vetting practiced by the Dutch. The protocol's original investigators have recently expressed concern that the interventions they described have been widely adopted on four continents without several of the protocol's essential discriminatory features (de Vries, 2020).

The extensive multi-year multidisciplinary evaluations of the children have been abbreviated or simply bypassed. The medical sequence is routinely used for children with post-pubertal onset of transgender identities complicated by mental health comorbidities (Kaltiala-Heino et al., 2018), and not just for those high-functioning adolescents with persistent early life cross-identifications, as was required by the Dutch protocol (de Vries & Cohen-Kettenis, 2012). Further, it has become increasingly common to socially transition children before puberty (Olson, Durwood, DeMeules, & McLaughlin, 2016), even though this was explicitly discouraged by the Dutch protocol at the time (de Vries & Cohen-Kettenis, 2012).

In addition, medical transition is frequently initiated much earlier than recommended by the original protocol (de Vries & Cohen-Kettenis, 2012). The authors of the protocol were aware that most children would have a spontaneous realignment of their gender identity with sex by going through early- to mid-stages of puberty (Cohen-Kettenis, Delemarre-van de Waal, & Gooren, 2008). The average age of initiating puberty blockade in the Dutch study was around 15. In contrast, currently the age limit has been lowered to the age of Tanner stage II, which can occur as early as 8-9 years (Hembree et al., 2017). Irreversible cross-sex hormones, initiated in the Dutch study at the average age of nearly 17, are currently commonly prescribed to 14-year-olds, and this lower age threshold has been recommended by WPATH Standard of Care 8 draft, the final version of which is due to be released in early 2022. The fact that children are transitioned before their identity is tested against the biological reality and before natural resolution of gender dysphoria has had a chance to occur is a major deviation from the original Dutch protocol. Systematic follow-up, reassessments, and tracking and publishing of outcomes are not performed.

As the lead Dutch researchers have begun to call for more research into the novel presentation of gender dysphoria in youth (de Vries, 2020; Voorzij, 2021) and question the wisdom of applying the hormonal and surgical treatment protocols to the newly presenting cases, many recently educated gender specialists mistakenly believe that the Dutch protocol proved the concept that its sequence helps all gender-dysphoric youth. Although aware of the Dutch study's importance, they seem to be unaware of its agreed upon limitations, and the Dutch clinicians' own discomfort that most new trans-identified adolescents presenting for care today significantly differ from the population the Dutch had originally studied. These facts, of course, underscore the need for a robust informed consent process.

The recommendations for informed consent process for children, adolescents, and young adults

Consent for all stages of gender transition should be explicit, not implied

Noninvasive medical care or care that carries little risk of harm does not require a signed informed consent document; rather, consent is implied through the act of a patient presenting for care. For example, when a parent brings in a child for a skin laceration or abscess, consent for sutures or simple incision and drainage is implied. Similarly, when a child presents with pneumonia and is hospitalized, consent for chest x-ray, IV fluids, and antibiotics is also implied. It is assumed that patients or their guardians agree to the interventions and understand the benefits and risks. When risks are greater, such as prior to surgery, chemotherapy, or another invasive procedure, an informed consent document is signed. Such situations require an explicit, or express informed consent.

In the context of interventions for gender dysphoria or gender incongruence, the uncertainties associated with puberty blocking, cross-sex hormones, and gender-affirmative surgeries are well-recognized (Manrique et al., 2018; National Institute for Health & Care Excellence, 2020a; 2020b; Wilson et al., 2018). In these cases, consent should be explicit rather than implied because of the complexity, uncertainty, and risks involved.

Informed consent for social transition represents a gray area. Evidence suggests that social transition is associated with the persistence of gender dysphoria (Hembree et al.,

2017; Steensma, McGuire, Kreukels, Beekman, & Cohen-Kettenis, 2013). This suggests that social gender transition is a form of a psychological intervention with potential lasting effects (Zucker, 2020). While the causality has not been proven, the possibility of iatrogenesis and the resulting exposure to the risks of future medical and surgical gender dysphoria treatments, qualifies social gender transition for explicit, rather than implied, consent.

Full unbiased disclosure of benefits, risks and alternatives is requisite

When mental health professionals are involved in evaluations and recommendations, the informed consent process begins either as part of an extended evaluation or is integrated in a psychotherapeutic process, separately or together, with the parents and patient. When pediatricians, nurse practitioners, or primary care physicians perform the initial evaluation, the informed consent process is more likely to be labeled as such in a briefer series of meetings.

In all settings, the informed consent discussions for gender-affirmative care should include three central ideas:

1. The decision to initiate gender transition may predispose the child to persist in their transgender identity long-term.
2. Many of the physical changes contemplated and undertaken are irreversible.
3. Careful long-term studies have not been done to verify that these interventions enable better physical and mental health or improved social functioning, or that they do not cause harm.

The informed consent process, culminating with a signed document, signifies that parents and patient have been educated about the short- and long-term risks, benefits and uncertainties associated with all relevant stages of the gender-affirmative interventions. The process must also inform the patients and families about the full range of alternative treatments, including the choice of not socially or medically treating the child's or adolescent's current state of gender/body incongruence.

Decisional capacity to consent needs to be assessed and family should be involved

Trans-identified youth typically present themselves as strongly desiring hormones and ultimately, surgery. It should not be assumed that their eagerness is matched with the capacity to carefully consider the consequences of their realized desires. Trans-identified youth younger than the age of consent should be part of the informed consent process, but they may not be mature enough to recognize or admit their concerns about the proposed intervention. For this reason, it is the parents who, after careful consideration, are responsible for signing an informed consent document.

The issue of the exact age at which adolescents are mature enough to consent to gender transition has proven contentious: courts have been asked to decide about competence to consent to gender-affirmative hormones for youth in the United Kingdom and Australia (Ouliaris, 2021). In the United States, the legal age for medical consent for gender-affirmative interventions varies by state.

When patients are age 18 and older, and in some jurisdictions as young as age 15 (Right to medical or dental treatment without parental consent, 2010), they do not legally require parental approval for medical procedures. But because an individual's change of gender has profound implications for parents, siblings, and other family members, it is usually prudent for clinicians to seek their input directly or indirectly during the informed consent process. This is done by requesting a meeting with the parents.

A recent study by a Dutch research team attempted to evaluate the decisional capacity of adolescents embarking on gender transition (Vrouenraets, de Vries, de Vries, van der Miesen, & Hein, 2021). The researchers administered the MacCAT-T tool, comprised of the *understanding*, *appreciating*, *reasoning*, and *expressing a choice* domains, to 74 adolescents who were 14.7 years old on average (with the minimum age of 10). They concluded that the adolescents were competent to consent to starting pubertal suppression, calling for similar research for the <12 group, particularly because "birth-assigned girls … may benefit from puberty suppression as early as 9 years of age" (Vrouenraets et al., 2021 p.7).

This study suffers from two significant limitations involving the MacCAT-T tool. It was never designed for children. Rather, it was designed to assess medical consent capacities of adults suffering from conditions such as dementia, schizophrenia, and other psychiatric disorders. There is a fundamental lack of equivalency between consenting to treatment by adults with cognitive impairments and obtaining consent from healthy children whose age-appropriate cognitive capacities are intact, but who lack the requisite life experiences to consent to profound life-changing medical interventions. We doubt, for example, whether even highly intelligent children who have not had sexual experiences can meaningfully comprehend the loss of future sexual function and reproductive abilities.

In addition, even for adults, the MacCAT-T tool has been criticized for its exclusive focus on cognitive aspects of capacity, failing to account for the non-cognitive aspects such as values, emotions and other biographic and context specific aspects inherent in the complexity of the decision process in real life (Breden & Vollmann, 2004). Children's values and emotions undergo tremendous change during the process of maturation.

The authors' conclusion about their young patients' competence to consent should be compared with what a panel of judges wrote in the challenge to the Tavistock treatment protocol (Bell v Tavistock, 2020):

> …the clinical intervention we are concerned with here is different in kind to other treatments or clinical interventions. In other cases, medical treatment is used to remedy, or alleviate the symptoms of, a diagnosed physical or mental condition, and the effects of that treatment are direct and usually apparent. The position in relation to puberty blockers would not seem to reflect that description. [para 135]
>
> …we consider the treatment in this case to be in entirely different territory from the type of medical treatment which is normally being considered. [para 140]
>
> … the combination here of lifelong and life changing treatment being given to children, with very limited knowledge of the degree to which it will or will not benefit them, is one that gives significant grounds for concern. [para 143]

It seems clear that perceptions of children as young as 10 years of age as medically competent vary by country, state, and the institution where the doctor works, and, by clinicians' beliefs about the long-term benefits of these interventions. We maintain that the claim that children can consent to extremely life-altering intervention is fundamentally a philosophical claim (Clark & Virani, 2021). Our view in this matter is that consent is primarily a parental function.

Informed consent should be viewed as a process rather than an event

Most institutions that care for transgender-identified individuals have devised obligatory consent forms that outline the risks and uncertainties of hormonal and surgical gender-affirmative interventions. However, the requisite signatures are frequently collected in a perfunctory manner (Schulz, 2018), akin to signatures collected ahead of a common surgical procedure. The purpose of such informed consent documents appears to be to protect practitioners from lawsuits, rather than attend to the primary ethical foundation of the process.

Although obtaining the signatures is important, the signed document should signify that the process of informed consent has been undertaken over an extended time period and is not simply quickly completed (Vrouenraets et al., 2021). We believe the latter approach poses an ethical concern (Levine, 2019).

The internal dynamics of the trans-identified young person and their families vary considerably. Parental capacities, their private marital and intrafamilial relationships, their cultural awareness, religious and political sensibilities all influence the amount of time necessary to undertake a thorough informed consent process. It is not prudent to suggest a specific duration for the process of informed consent, other than to emphasize that it requires a slow, patient, thoughtful question and answer period as the parents and patient contemplate the meaning of what is known and unknown and whether to embark on alternative approaches to the management of gender dysphoria before the age of full neurological maturity has been reached, mental health comorbidities have been addressed, and a true informed consent by the patient is more likely.

Final thoughts

Sixty years of experience providing medical and surgical assistance to transgender-identified persons have seen many changes in who is treated, when they are treated, and how they are treated. Today, the emphasis has shifted to the treatment of the unprecedented numbers of youth declaring a trans identity. As adolescents pursue social, medical, and surgical interventions, health care providers may experience unease about patients' cognitive and emotional capacities to make decisions with life-changing and enduring consequences. An unrushed informed consent process helps the provider, the parents, and the patient.

Three issues tend to obscure the salience of informed consent: conspicuous mental health problems, uncertainty about the minor's personal capacity to understand the irreversible nature of the interventions, and parental disagreement. Physical and psychiatric comorbidities can contribute to the formation of a new identity, develop as its consequence, or bear no connection to it. Assessing mental health and the minor's functionality is one of the reasons why rapid affirmative care may be dangerous for patients and their families. For example, when situations involve autism, learning disorders, sexual abuse, attachment problems, trauma, separation anxiety, previous depressed or anxious states, neglect, low IQ, past psychotic illness, eating disorders or parental mental illness, clinicians must choose between ignoring these potentially causative conditions and comorbidities and providing appropriate treatment before affirmative care (D'Angelo et al., 2020).

For youth less than the age of majority, informed consent via parents provides a legal route for treatment but it does not make the decision to socially transition, provide hormones, or surgically remove breasts or testes less fraught with uncertainty. The best that health professionals can do is to ensure that the consent process informs the patient and parents of the current state of science, which is sorely lacking in quality research. It is the professionals' responsibility to ensure that the benefits patients and parents seek, and the risks they are assuming, are clearly appreciated as they prepare to make this often-excruciating decision.

Young people who have reached the age of majority, but who have not reached full maturation of the brain represent a unique challenge. It is well-recognized that brain remodeling proceeds through the third decade of life, with the prefrontal cortex responsible for executive function and impulse control the last to mature (Katz et al., 2016). The growing number of detransitioners who had been old enough to legally consent to transition, but who no longer felt they were transgender upon reaching their mid-20's, raises additional concerns about this vulnerable age group (Littman, 2021; Vandenbussche, 2021).

When the clinician is uncertain whether a young person is competent to comprehend the implications of the desired treatment—that is, when informed consent cannot inform the patient—the clinician may need more time with the patient. When parents or guardians do

not agree about whether to use puberty blockers or cross-sex hormones, clinicians are in an uneasy spot (Levine, 2021). This occurs in both intact and divorced families. Australia has given legal instructions to clinicians facing these uncertainties: the court is to be asked to decide (Ouliaris, 2021). The court system in the UK has been grappling with similar issues in recent years. While it is a rare case that ends up in a courtroom, clinicians devoted to a deliberate informed consent process are still likely to encounter ethical dilemmas that they cannot resolve.

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Pasientsikkerhet for barn og unge med kjønnsinkongruens

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Personer med kjønnsinkongruens og kjønnsdysfori har ulike ønsker og behov for helsetjenester. Mange lever godt med sin kjønnsinkongruens og håndterer denne uten helsehjelp, og andre ønsker og trenger helsehjelp. (Se ordliste i kapittel 13 for ordforklaringer)

Når Ukom går inn i temaet kjønnsinkongruens, ser vi på hvordan pasientsikkerheten er ivaretatt i hjelpe- og behandlingstilbud for kjønnsinkongruens og kjønnsdysfori. Vårt formål med undersøkelsen er å sikre trygg hjelp og behandling for barn og unge med kjønnsinkongruens.

Det pågår en offentlig debatt om behandlingstilbud for kjønnsinkongruens. Dette er krevende, og mange vegrer seg for å delta i debatten. Det kan være utfordrende og vanskelig å delta fordi uenighetene er store både mellom grupper og innad i grupper. Vi ser at ordvalg og forståelse for kompleksiteten er viktig. Situasjonen med utrygghet og uenighet påvirker utviklingen av helsetjenestetilbudet.

I vår rapport har vi forsøkt å løfte frem ulike perspektiv. Samtidig er det viktig for oss å være tydelige på våre funn. Det vil si hva som utfordrer pasientsikkerheten. Mange har jobbet og jobber med å stadfeste og bygge et godt helsetilbud for personer med kjønnsinkongruens og kjønnsdysfori, både nasjonalt og internasjonalt. Ukoms rapport bygger videre på dette arbeidet. Vi påpeker at dette feltet nå trenger et løft for å bedre pasientsikkerheten, spesielt for den helsehjelpen som skal gis til barn og unge i Norge.

Sammendrag

Ukom har gjennomført en undersøkelse av behandlingstilbudet til barn og unge med kjønnsinkongruens. Bakgrunnen var varsler direkte til Ukom fra pårørende som stiller spørsmål ved flere forhold knyttet til pasientsikkerheten. Flere aktører, både fra myndighetssiden, helsepersonell og pasient- og pårørendeorganisasjoner stiller spørsmål ved forsvarligheten og organiseringen av behandlingstilbudet.

Rapporten omhandler barn og unge generelt. Det har vært en stor økning i henvendelser til helsetjenesten fra personer med kjønnsinkongruens de siste årene. Spesielt har antallet barn og unge i tenårene som søker seg til, eller blir henvist til vurdering og behandling i spesialisthelsetjenesten, økt betydelig. Den største økningen er blant ungdommer og unge voksne som er registrert jente ved fødsel, men identifiserer seg som gutter. Vår oppmerksomhet har derfor spesielt vært rettet mot tenåringer og unge med kjønnsinkongruens og kjønnsdysfori som søker helsehjelp. Barn og unge er ikke ferdig utviklet kroppslig, mentalt, seksuelt eller sosialt. Det fordrer særskilt årvåkenhet med tanke på pasientsikkerheten. Våre funn og anbefalinger vil også være aktuelle for tilbudet til voksne.

Vi har i rapporten delt våre funn inn i seks hovedområder:

Utilstrekkelig kunnskap

Kunnskapsgrunnlaget, spesielt forskningsbasert kunnskap for kjønnsbekreftende behandling (hormonell og kirurgisk), er mangelfullt og langtidseffektene er i liten grad kjent. Dette gjelder særlig for tenåringspopulasjonen der stabiliteten til deres kjønnsinkongruens heller ikke er kjent. Det mangler forskningsbasert kunnskap om behandling av pasienter med ikke-binær kjønnsinkongruens. For å ivareta pasientsikkerheten vurderer Ukom det nødvendig at kunnskapsgrunnlaget om kjønnsinkongruens og kjønnsdysfori styrkes, og at helsetjenestetilbudet innrettes i tråd med kunnskapsgrunnlaget.

Overordnet styring - en retningslinje med annerledes bakgrunn

Helsedirektoratets nasjonale faglige retningslinje for kjønnsinkongruens legger føringer for helsetjenestetilbudet. Den konsentrerer seg om organisering, likeverd og rettigheter. Dette kan ha vært viktig på det tidspunktet retningslinjen ble utarbeidet, fordi det var nødvendig å stadfeste helsetjenestetilbudet til personer som opplever kjønnsinkongruens. Samtidig vurderer vi at å fravike kravet om utvikling av kunnskapsbaserte retningslinjer, har skapt rom for usikkerhet og sprikende forventninger. Helsepersonell har fått store muligheter til tolkning innenfor et relativt smalt fagområde som mangler systematisk kunnskapsoppsummering i Norge. Retningslinjen gir rettigheter uten å avklare spørsmål knyttet til prioritering og forsvarlighet. Dette er krevende for helsepersonellet som forvalter tjenestene i det daglige.

Krav til forsvarlighet – særlig knyttet til barn og unge

Den nasjonale faglige retningslinjen for kjønnsinkongruens er lite normerende. Den stiller ikke spesifikke krav til utredning eller krav til medisinsk indikasjon for oppstart av behandling. Omtalen av barns samtykkekompetanse og foreldres rett til informasjon gir rom for tolking. Retningslinjen etablerer ikke tilstrekkelig standard for helsetjenestetilbudet, og vi mener det for noen pasienter kan utgjøre en pasientsikkerhetsrisiko. Dette kan gå utover forsvarlighetskravet som har bred forankring i helselovgivningen, og kan også være krevende for tilsynsmyndighetene.

Rett til helsehjelp – et gap i forventninger

Vår undersøkelse tyder på at det er et gap mellom det retningslinjen skisserer og det som er mulig, gitt dagens tilgjengelige tilbud og kunnskapsgrunnlag. Den nasjonale faglige retningslinjen skaper forventninger hos pasientene som helsetjenesten i liten grad kan innfri. Dette gjelder blant annet retten til spesialisthelsetjenester. Det er vanskelig for tjenesten å innfri forventningene uten at kunnskapsgrunnlaget er godt dokumentert, og uten at det er god oversikt over eventuelle negative og skadelige sider ved de ulike behandlingene. Dersom det stilles krav om å bruke prinsipper for utprøvende behandling vil det gi rammer som sikrer informasjon, grundig oppfølging og bidra til mer kunnskap.

Hjelpe- og behandlingstilbudet - variasjon i praksis og kompetanse

Det er stor variasjon i hvilke tilbud og hvilken kompetanse som tilbys ulike steder i landet. Det er fare for både under-, over- og feilbehandling av barn og unge med kjønnsinkongruens og kjønnsdysfori. I tillegg ser vi at det er utfordringer med å etablere et desentralisert tilbud på et smalt og komplekst fagfelt. For å styrke tilbudet mener Ukom at det er viktig å styrke helsetjenestetilbudet i primærhelsetjenesten, bygge økt tverrfaglig spisskompetanse i spesialisthelsetjenesten på regionalt nivå og sikre at den nasjonale behandlingstjenesten har tilstrekkelig kapasitet til dagens pågang.

Ytringsklima og samhandling

Vi ser at det på kjønnsinkongruensfeltet har utviklet seg et krevende ytringsklima. Ytringsklimaet i det offentlige rom påvirker tilgjengelig informasjon for barn og unge med kjønnsinkongruens og kjønnsdysfori og deres familier. Det er betydelig påvirkning på barn og unge, også relatert til behandling og helsetjenester. Vi hører om frykt og redsel for å trå feil fra alle hold. Ulike meninger om hva som er rett behandling kan gi et vanskelig krysspress. Forskjellig vektlegging og omtale av hva som er nødvendig på gruppenivå kan forvirre og ødelegge for pasient-behandlerforhold og en persontilpasset tilnærming for den det gjelder. Det er behov for å etablere et konstruktivt felleskap for alle som er engasjert i god helsehjelp til personer med kjønnsinkongruens.

Ukom anbefaler

Vi er opptatt av at barn og unge med kjønnsinkongruens har et trygt og forsvarlig helsetjenestetilbud. Vi kommer derfor med anbefalinger som kan bidra til at denne gruppen på sikt får et bedre og sikrere helsetjenestetilbud. Våre anbefalinger er knyttet til revidering av retningslinjen, trygge rammene for behandling som tilbys barn og unge og tiltak for å styrke kunnskapsgrunnlaget. Anbefalingene vil også bidra til systematisk innsamling av data og fremme følgeforskning. Det er viktig at barn og unge med kjønnsinkongruens og kjønnsdysfori, inklusive ikke-binære, blir forsvarlig ivaretatt mens utviklingen av helsetjenestetilbudet pågår.

Ukom anbefaler:

1. at Helse- og omsorgsdepartementet gir Helsedirektoratet i oppdrag å revidere Nasjonal faglig retningslinje, Kjønnsinkongruens. Revideringen må blant annet være basert på en systematisk kunnskapsoppsummering. Vi peker på flere momenter som bør inngå i revisjonen.
2. at pubertetsutsettende behandling (pubertetsblokkere) og hormonell og kirurgisk kjønnsbekreftende behandling for barn og unge defineres som utprøvende behandling. Dette er særlig viktig for tenåringer med kjønnsdysfori.
3. at Helse- og omsorgsdepartementet vurderer om det bør opprettes et nasjonalt medisinsk kvalitetsregister for behandling av barn og unge med kjønnsinkongruens og kjønnsdysfori. Nødvendige tiltak må settes i verk for at et slikt nasjonalt kvalitetsregister kan etableres, driftes og finansieres for å bidra til oversikt, bedre kvalitet og redusere uberettiget variasjon i pasientbehandlingen.

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RESEARCH ARTICLE

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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Abstract

Background

In adolescents with severe and persistent gender dysphoria (GD), gonadotropin releasing hormone analogues (GnRHa) are used from early/middle puberty with the aim of delaying irreversible and unwanted pubertal body changes. Evidence of outcomes of pubertal suppression in GD is limited.

44 1-15 yo's on PB
Bone mineral content and density

Methods

CBCL, YSR,

We undertook an uncontrolled prospective observational study of GnRHa as monotherapy in 44 12–15 year olds with persistent and severe GD. Prespecified analyses were limited to key outcomes: bone mineral content (BMC) and bone mineral density (BMD); Child Behaviour CheckList (CBCL) total t-score; Youth Self-Report (YSR) total t-score; CBCL and YSR self-harm indices; at 12, 24 and 36 months. Semistructured interviews were conducted on GnRHa.

44 were followed to 12 month
24 to 24 months
12 to 36 months
HUGE drop out rate

Only one ceased PB's, all went onto CSH

Results

44 patients had data at 12 months follow-up, 24 at 24 months and 14 at 36 months. All had normal karyotype and endocrinology consistent with birth-registered sex. All achieved suppression of gonadotropins by 6 months. At the end of the study one ceased GnRHa and 43 (98%) elected to start cross-sex hormones.

There was no change from baseline in spine BMD at 12 months nor in hip BMD at 24 and 36 months, but at 24 months lumbar spine BMC and BMD were higher than at baseline (BMC +6.0 (95% CI: 4.0, 7.9); BMD +0.05 (0.03, 0.07)). There were no changes from baseline to 12 or 24 months in CBCL or YSR total t-scores or for CBCL or YSR self-harm indices, nor for CBCL total t-score or self-harm index at 36 months. Most participants reported

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positive or a mixture of positive and negative life changes on GnRHa. Anticipated adverse events were common.

Conclusions

Overall patient experience of changes on GnRHa treatment was positive. We identified no changes in psychological function. Changes in BMD were consistent with suppression of growth. Larger and longer-term prospective studies using a range of designs are needed to more fully quantify the benefits and harms of pubertal suppression in GD.

Introduction

Gender dysphoria (GD) describes the experience of incongruence between an individual's experienced gender and the sex they were assigned at birth. GD [1] in children and young people, also known as Gender Incongruence [2] and previously known as Gender Identity Disorder (GID), is associated with considerable distress or impairment in social, school or other important areas of functioning [3,4]. Interventions include psychosocial support, therapy and medical or surgical interventions to align the body with the identified gender [3,5]. Terminology in this field can be challenging [6]. Here we use birth-registered sex to refer to the sex assigned at birth by clinicians based upon external genitalia [6]. Gender identity refers to a young person's personal sense of their gender. We use the terms 'continuation' and 'discontinuation' to refer to GD across childhood and adolescence.

GD in adolescence is highly likely to continue into adult life where gender dysphoria persists after the onset of puberty [3]. Those with earlier onset or more intense GD and those in whom the development of secondary sexual characteristics in puberty is associated with increasing gender dysphoria or psychological distress are more likely to have persistent GD [3,7]. In adolescents with severe and persistent GD, international [8] and national [9–11] guidelines recommend the use of treatments to suppress the rise in sex hormones (oestradiol or testosterone) in young people during puberty. Gonadotropin releasing hormone analogues (GnRHa) are synthetic peptides that work by stimulating gonadotropin release in a tonic fashion which desensitises the gonadotropin receptors, resulting in reversible suppression of sex hormone production.

In GD, GnRHa can be used from the early/middle stages of puberty with the aim of delaying irreversible and unwanted pubertal body changes and giving young people the opportunity to explore their gender identity during a period when puberty is not advancing [3]. This period also allows clinicians more time to assess the stability of young people's gender identity [6]. Despite this treatment being given in mid-puberty it is also called early puberty suppression, where 'early' refers to earlier than the historic practice of suppression after completion of puberty.

Pubertal suppression is currently practised in the majority of international centres across Europe, the Americas and Australasia, as evidenced by a recently published survey of 25 international centres by the European Society of Paediatric Endocrinology (ESPE) [12]. Pubertal suppression with GnRHa as monotherapy is a time-limited strategy, due to the potential for side effects with long-term use. In the UK, for those commencing under age 15 years, use of GnRHa alone ceases after 16 years when young people face a decision to return to the sex hormones produced by their body or begin cross-sex hormones [5]. There are limited data on the outcomes of pubertal suppression in the treatment of young people with GD [3,13]. A recent

systematic review included data on the physical and mental health outcomes of pubertal suppression using GnRHa in over 500 young people [4]. Longer-term follow-up data on pubertal suppression in GD are limited to individuals from four cohorts [14–19].

In 2011 a study was begun to evaluate the proximal outcomes of mid-pubertal suppression using GnRHa in young people with persistent GD (see http://gids.nhs.uk/our-early-intervention-study). Use in the UK began after mid-pubertal suppression had been incorporated into international guidelines [20] and had become available in the USA [21,22], the Netherlands [15], Australia [23] and a number of European countries. The Gender Identity Development Service (GIDS) at the Tavistock and Portman NHS Foundation Trust, London, is a national service for children and young people with GD, drawing from England, Wales and Ireland. Mid-pubertal suppression was offered by the GIDS from 2011 initially only within an ethically approved uncontrolled observational research study with prospective data collection, where all participants received GnRHa. We anticipated that we would recruit 10–15 young people per year for 3 years and follow them up to the end of monotherapy with GnRHa. At the time, a randomised controlled study was not considered feasible due to very small numbers and inability to retain participants in the control arm, as the control treatment would have resulted in progression into near complete puberty and an increasing number of UK families were accessing mid-pubertal suppression internationally. Allocation blinding was also not considered feasible in young people using a product requiring monthly injections.

Here we describe the short-term outcomes of 44 young people with GD from this research cohort, recruited aged 12–15 years and followed to the end of GnRHa monotherapy after age 16 years. This paper describes their medical, psychological and social outcomes during the GnRHa treatment pathway up to the point of decisions about whether or not to undertake further physical treatment. The aims of the study as defined at inception in 2011 were:

1. To evaluate the benefits and risks for physical and mental health and wellbeing of mid-pubertal suppression in adolescents with GD
2. To add to the evidence base regarding the efficacy of GnRHa treatment for young people with GD
3. To evaluate continuation and discontinuation of GD and the continued wish for gender reassignment within this group.

Methods

We undertook an uncontrolled prospective observational study of GnRHa monotherapy in a highly selected group of young people with persistent and severe GD.

Participants

The cohort consisted of 44 sequentially eligible young people, aged 12 to 15 years, who were recruited between April 2011 and April 2014 and who commenced GnRHa treatment between June 2011 and April 2015. They were all recruited from patients referred to the GIDS.

Eligibility criteria were chosen to match those used for a Netherlands cohort [24], namely that the young person:

A. is aged 12–15 years

B. Psychological criteria

1. has been seen by the GIDS for at least 6 months and attended at least 4 interviews for assessment and therapeutic exploration of their gender identity development.

2. psychological stability sufficient to withstand the stresses of medical treatment for GID.
3. fulfils the following criteria relating to GID:
   a. Throughout childhood (defined as over 5 years) the adolescent has demonstrated an intense pattern of cross-gendered behaviours and cross-gender identity.
   b. The adolescent has gender dysphoria that is significantly increased with the onset of puberty. Following assessment the clinician(s) working with the young person deem that there is a high likelihood of the young person experiencing severe psychological distress consequent on experiencing full pubertal development before pubertal suppression is implemented.
4. The young person and their parents/guardians are actively requesting pubertal suppression.
5. is able to give informed consent.

C. Physical/medical criteria

1. is in established puberty:
   - For birth-registered males Tanner (genital and pubic hair (PH)) stage 3 and above.
   - For birth-registered females Tanner (breast and PH) stage 2 and above.
     The rationale for the sex difference was that the pubertal growth spurt which early intervention aims to avoid occurs typically two years earlier in females (Tanner stage 2–3) than in males (Tanner stage 3–4), thus earlier intervention is required in females.
2. has normal endocrine function and karyotype consistent with birth registered sex.

Note that the presence of mildly elevated androgens in birth registered females consistent with polycystic ovarian syndrome is not an exclusion criterion.

Exclusion criteria:

1. Inability to participate with full investigatory protocol e.g. needle phobia, failure to attend for tests and scans.
2. Body mass index (BMI) <2nd centile for age and birth-registered sex [20].
3. Serious psychiatric conditions (e.g. psychosis, bipolar condition, anorexia nervosa, severe body-dysmorphic disorder unrelated to GD).
4. Inability to give informed consent according to the Fraser/Gillick guidelines.
5. Low spine or hip bone mineral density (BMD) on DXA scan: more than 2 SD below expected BMD for age and birth-registered sex. In exceptional circumstances a low BMD was acceptable if:
   i. it was felt to be clinically appropriate by the treating clinicians, who felt that on the balance of risks, pubertal suppression was justified despite the later risk of osteoporosis
   ii. the young person and parents understood the risks of GnRHa treatment for bone density (i.e. potential risks of later osteoporosis)
   iii. The young person and parents consented to more frequent monitoring of BMD (repeat DXA scans 6 months after starting GnRHa and yearly thereafter while on GnRHa) despite the small DXA radiation dose

iv. The young person and parents consented to stopping treatment if raw BMD fell whilst on GnRHa.

The treatment

The treatment under study was suppression of puberty using the GnRHa *triptorelin* together with psychosocial support and therapy, from study entry until the end of the GnRHa monotherapy pathway at age 16 years or older. GnRHa monotherapy ceased when young people either started cross-sex hormones (and continued on GnRHa) or stopped GnRHa. Treatment duration was therefore from 1 to 4 or 5 years depending on age at study entry. Consenting young people were given triptorelin 3.75mg by intramuscular injection every 28 days during the treatment period. Two participants who found monthly injections difficult were moved to a ten-weekly preparation of 11.25mg of triptorelin. The aim of treatment was to suppress gonadotropins and sex hormones to near pre-pubertal levels [13]. Continued regular attendance for psychological support and therapy throughout the study was a precondition of GnRHa prescription. In addition local psychological services provided support for co-occuring difficulties for participants as required.

Procedures and pathway

All young people and families attending the GIDS during the study period were provided with an information leaflet about research underway within the unit. Those wishing to find out more about the study discussed it with their GIDS clinicians and those deemed likely to be eligible were given detailed written study information. Those wanting to participate were invited to a medical clinic at UCLH for an initial discussion. At the first medical clinic, young people and families were seen by a senior paediatric endocrinology clinician together with a senior GIDS clinician, who discussed with the family the then current state of knowledge and rationale for treatment, eligibility criteria and potential risks and benefits of participation. Risks included the anticipated side-effects of GnRHa treatment including symptoms resulting from the withdrawal of sex steroids (headaches, hot flushes), fatigue, loss of libido and low mood, the potential that treatment could influence the continuation of their GD and the potential for unknown risks. It was emphasised that young people needed to continue with both regular medical and psychosocial follow-up during the study and that treatment would cease if they did not comply with the treatment or monitoring requirements. A full medical history was elicited and the clinicians also reviewed a summary of the psychological history and assessment from the GIDS. In this visit information sheets were re-provided if families had lost them or forgotten details of the study. If young people and families remained interested in participation, medical investigations were organised and families were invited for a repeat discussion and a formal evaluation of eligibility at a second medical clinic visit approximately 3 months later. Families were asked to think about the issues raised in the meeting and to discuss with their GIDS clinicians if necessary, in order to discuss further at the second visit.

At the second medical clinic visit, the same clinicians repeated the discussion of risks and benefits and explored understanding with the young person and family. A chaperoned medical examination was undertaken including pubertal assessment and the results of medical investigations were reviewed. Endocrine and GIDS clinicians jointly reviewed eligibility and offered participation in the study to those deemed eligible.

The implications of treatment for fertility were discussed at the first and second medical visits and all young people were urged to consider storing gametes before starting GnRHa. Access to storage depended on regional availability within the NHS. Note that counselling on fertility

continued across the study, and clinicians periodically checked with young people who had decided against storage whether they wished to revisit their decision.

Informed consent was obtained in writing from both the young person and a parent or carer holding parental responsibility. The ability of the young person and parents to give informed consent was assessed jointly by the senior adolescent endocrine and GIDS clinicians, informed by written notes from the GIDS team. The consent forms were read with the young person and the parent by the clinicians to be sure they fully understood the information on the forms before signing.

48 young people and families attended the medical clinics for discussion of participation in the trial, of whom 44 wished to participate. Eight young people (7 birth assigned males) were not eligible for participation at the second medical visit as they were not yet sufficiently advanced in puberty. They were followed up every 3–6 months and entered the study subsequently when sufficiently advanced in puberty (median waiting time 7 months).

The date of signing the consent form was taken as the start of study treatment, although it frequently took one to three months for GnRHa treatment to start due to administrative requirements. Participants were followed up in the endocrine clinic, 3–6 monthly in the first 18 months and 12-monthly thereafter, till the end of the treatment pathway, defined as the date on or after the 16th birthday when a decision was made to either cease GnRHa or start cross-sex hormones. The final participant completed the pathway in February 2019.

Outcomes

The following data were collected:

A. Baseline explanatory variables

1. Sex and gender: Young people were classified by their sex assigned at birth (birth-registered sex) and self-identified gender.
2. Ethnicity: Ethnicity was obtained from clinic records. For analysis, ethnicity was grouped as white, South Asian, black or mixed.
3. Puberty: Pubertal status at baseline was classified using information on genital/breast and pubic hair Tanner stages as appropriate. This was summarized into a single pubertal stage, with the breast/genital stage taking precedence if there was discrepancy between breast/genital and public hair stage.
4. Clinical data: These consisted of a) identification of normal phenotype on physical examination for birth-registered sex; b) venepuncture assessment of endocrinology (gonadotropins, prolactin, oestrogen or testosterone, adrenal androgens, thyroid function; and a short synacthen test in birth-registered females only), karyotype, full blood count, renal and liver function, calcium and vitamin D; and c) imaging including wrist bone age and (in birth-registered females only) pelvic ultrasound scan. Medical assessment at baseline and follow-up was consistent with Endocrine Society guidelines [8,20].

B. Study outcomes

Study outcomes concerned domains including response to treatment, bone health, safety indicators and adverse events, psychological function; participant experience and satisfaction; and decisions regarding treatment following GnRHa. Outcome data were collected at routine clinic visits to GIDS or medical clinics at UCLH and timings therefore varied. For the purposes of these analyses, data for each participant were assigned to baseline (before treatment) and to the closest of the following outcome periods: 12, 24, 36 and 48 months on treatment. For safety and response to pubertal suppression outcomes, data were also examined at 6 months.

1. Response to pubertal suppression

Gonadotropins (LH, FSH), testosterone (in birth-registered males) and oestrogen (birth-registered females) were measured after venepuncture. Height, weight and blood pressure were recorded by trained clinic staff. BMI z-score for age and birth-registered sex was calculated [25]. Menarcheal status and presence/absence of menstrual periods was obtained by report from birth-registered females.

2. Bone health

Bone mineral content (BMC) and bone mineral density (BMD) in the lumbar (L1 to L4) spine and hip (total hip) were measured by dual energy X-ray absorptiometry (DEXA) scans using a Hologic Discovery QDR series model 010–1549 (Hologic Inc, Bedford, MA, USA). BMD z-scores for age and birth-registered sex appropriate to this machine were calculated [26]. BMD z-scores for spine and hip were further adjusted for height (height-adjusted z-scores) using published formulae [27].

3. Safety indicators and adverse events

Blood samples were collected by venepuncture for liver and renal function, full blood count, calcium and vitamin D, prolactin, adrenal androgens and thyroid function. Participants were routinely questioned about adverse events at medical clinic visits, including anticipated events such as headaches, hot flushes or fatigue plus any other unanticipated events.

4. Psychological function

Psychological outcomes included a clinical outcome routinely collected after GIDS appointments and a range of outcomes assessed using questionnaires. A standardised set of psychological questionnaires used in the GIDS clinic was completed at the time young people were deemed potentially eligible and referred to the medical clinic. Questionnaires were completed at home by the young person and parent between GIDS clinical meetings, and a research assistant followed up families to ensure their completion. Questionnaires were repeated approximately every 12 months on treatment.

i. General psychological functioning

The Child Behaviour Checklist (CBCL) (parent report) and Youth Self Report (YSR) (self-report) are general measures of psychological functioning and part of the Achenbach System of Empirically Based Assessment (ASEBA; www.aseba.org). The CBCL consists of 113 questions and is validated for children aged 6–18 years in international population samples [28]. The YSR consists of 112 questions and is validated in international populations of young people aged 11–18 years [29]. Questions in both are scored on a three-point Likert scale (0 = absent, 1 = occurs sometimes, 2 = occurs often), with the time frame for item responses being the past six months. Scoring for both instruments provides a total problems score, an internalizing problems score (items which assess anxious/depressed, withdrawn-depressed, and somatic complaints) and an externalizing score (focusing on rule-breaking and aggressive behaviours). Each questionnaire was scored with Assessment Data Manager Software using ASEBA standard norms and t-scores were generated based on reference data for birth-registered sex and broad age-ranges (here 12–18 years). Higher scores indicate greater morbidity. To account for normative change within our age-range, we used international reference data [29] to transform YSR raw scores into z-scores for year of age. As reference data from the UK were not available, reference data from both Australia and the Netherlands were used.

ii. Self-harm index

Self-harm actions and thoughts were assessed through two questions in each of the CBCL (parent report) and YSR (self-report): Item 18 (I deliberately try to hurt or kill myself) and Item 91 (I think about killing myself). Possible responses for each question were 0 = not true, 1 = somewhat or sometimes true, or 2 = very true or often true. We followed previous studies in calculating a self-harm index score to avoid multiple statistical comparisons across

correlated categorical-response variables. The index was calculated as the sum of the two items in each scale to create an index from 0 to 4 for each of the CBCL and YSR [30–32], a higher score indicating greater self-harm thoughts and behaviour.

iii. Health related quality of life (HRQoL)

This was assessed through separate young person and parent Kidscreen-52 questionnaires, each consisting of 52 items which assess HRQoL across ten dimensions: physical well-being; psychological well-being; moods and emotions; self-perception; autonomy; relations with parents and home life; social support and peers; school environment; social acceptance (bullying); and financial resources. All items use five-point Likert-style scales to assess either the frequency (never-seldom-sometimes-often-always) of certain behaviours/feelings or the intensity of an attitude (not at all–slightly-moderately-very-extremely). The measure was developed for young people aged 8–18 years, with the recall period of one week. The questionnaires provide scores in the form of continuous t-scores for the ten subscales derived from a multinational European sample [33]. Lower scores indicate lower HRQoL, i.e. greater morbidity.

iv. Body image

The Body Image Scale (BIS) is a self-report measure of 30 items used to assess body image satisfaction or dissatisfaction validated for age 12+. The instrument considers 30 body features which the respondent is asked to rate in terms of satisfaction on a five-point scale (1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied). The BIS provides a total score in the form of a continuous score for the total scale as well as for three subscales assessing primary sexual characteristics, secondary sexual characteristics and 'neutral' characteristics (i.e. non-sexual characteristics, e.g. nose) [34]. Higher scores represent higher degrees of body dissatisfaction.

v. Gender dysphoria

The Utrecht Gender Dysphoria Scale (UGDS) is a self-report measure used to assess the intensity of GD validated for age 12+. It comprises of 12 statements with agreement on a five-point scale (1 = agree completely, 2 = agree somewhat, 3 = neutral, 4 = disagree somewhat, and 5 = disagree completely). There are separate versions for birth-registered males and females. Items are summed to give a single total score, with higher scores indicating greater GD.

vi. Clinical outcomes

The Children's Global Assessment Scale (CGAS) is a rating of functioning in children and young people aged 6–17 years, extensively used as a routine clinical measure in child and adolescent mental health services in the UK. Treating clinicians assign young people a single score between 1 and 100, based on a clinician's assessment of a range of aspects related to a child's psychological and social functioning, with the time period being the previous month. Higher scores indicate better functioning, with categories ranging from 'extremely impaired' (1–10) to 'doing very well' (91–100) [35].

5. Participant experience and satisfaction with GnRHa

Young people were invited to participate in semi-structured qualitative interviews at 6–15 months and 15–24 months after starting GnRHa. Interviews were conducted in person or by telephone with a research assistant. If young people were unavailable, questions were posted to be completed and returned. The interview consisted of 12 questions related to changes young people had experienced in ten domains since starting on GnRHa: life overall, memory, focus, sense of direction, mood, energy levels, relationships with friends, relationships with family, gender role and sexuality. For each domain, young people were asked first about the general direction of change in that domain (whether changes were positive, neutral, negative or mixed positive and negative) and then asked for examples of changes experienced and why they assigned the chosen change rating. At the end of the interview two further questions were asked about change in any other experiences (i.e. allowing open ended responses) and whether

young people wished to continue on GnRHa treatment. Note there was no interview conducted before young people started GnRHa. Interviews were recorded in contemporaneous written notes by the researcher. The questionnaire is provided in the S1 Appendix.

6. Further treatment decisions

Decisions made at the end of the GnRHa pathway were recorded in terms of which if any further treatment for GD young people chose.

Note that other measures of gender dysphoria (Gender Identity Interview; Recalled Childhood Gender Identity Scale) were specified in our original protocol, however they were discontinued during the study as: a) they were historical instruments with poor construct validity and the binary references to male and female roles were challenging for some participants; and b) repeated questioning about gender dysphoria resulted in some distress to respondents. Our protocol had originally included the ASEBA Teacher Report Form (TRF), however we were unable to obtain data from teachers so this outcome was dropped. The Social Responsiveness Scale (SRS) was a baseline only assessment of autistic traits; these data will be analysed in the future.

Analysis plan

Analyses were conducted according to the Statistical Analysis and Dissemination Plan, lodged with the ethics committee that approved the study before the analysis started (see S2 Appendix: Statistical Analysis Plan). The analysis plan was designed to report data on all outcomes but to minimise the likelihood of chance findings due to the large number of outcomes and small sample size. Sample sizes necessarily varied across follow-up as young people were recruited at different ages (12–15 years) but left the study soon after their 16th birthday. All 44 participants had data at 12 months follow-up. As participants necessarily left the study soon after their 16th birthday, numbers reduced after 12 months follow-up as participants could no longer remain in the study. Note this does not represent drop-out. There were 24 left at 24 months, 14 at 36 months and 4 at 48 months. In view of this, outcome reporting was restricted to change from baseline to 12, 24 and 36 months. We made no attempt to account for missing data due to the small sample size and the likelihood of the data missing not at random.

We restricted analyses to primarily descriptive statistics, with formal statistical testing of change across the study restricted to six pre-specified outcomes, i.e.:

1. Overall psychological functioning
   a. parent report: CBCL total t-score
   b. young person self-report: YSR total t-score
2. Self-harm index
   a. parent report: CBCL self-harm index
   b. young person self-report: YSR self-harm index
3. Bone health
   a. BMD and BMC for lumbar spine
   b. BMD and BMC for hip

Assessment of change was through paired t-tests for normally distributed data and the Wilcoxon matched-pairs sign-rank test for non-normal data. The number of formal statistical tests conducted in the study was 16; with overall significance at $p = 0.05$ and a Bonferroni correction, the appropriate threshold for statistical significance is about $p = 0.003$.

In our results and conclusions we refer to change in outcomes only for those that were formally tested. Reporting for other continuous outcomes was restricted to mean and 95% confidence intervals (95%CI) or median and interquartile range (IQR). For categorical outcomes, simple proportions were reported. We reported laboratory tests as normal or abnormal based upon laboratory reference data for age, with the exception of gonadotropins. We did not report data where the sample size was less than 8.

Analysis of potential predictors of outcome was confined a priori to two factors, birth-registered sex and pubertal stage at baseline. Three pre-specified continuous outcomes were examined at 12 months, namely:

1. BMD for lumbar spine
2. YSR total t-score
3. CGAS score

Associations were examined using linear regression of follow-up score on baseline score, adding each baseline factor separately to the model and considering the interaction of predictor with baseline score. All analyses were conducted using Stata 16 (Statacorp, College Station TX).

Responses to the semi-structured interview questionnaires were analysed simply for thematic content in terms of the direction and amount of change that young people experienced in each domain. This involved coding responses about experiences since starting GnRHa into categories; i.e. either positive/improving, negative/deteriorating, both positive and negative, no change or not known. The question on change in sexuality was coded as yes change, no change or not known. Wishes to continue with GnRHa were coded as yes, no or don't know.

To compare our findings with the literature, we drew upon recent reviews [3,4,6,13] and updated a recent review [4] from 1 June 2017 to 31 December 2019 using the same search terms in Medline (see S1 Appendix).

Ethics

Ethical approval for the study was obtained from the National Research Ethics Service (NRES: reference 10/H0713/79) in February 2011. Study consent allowed the use of routinely collected clinical data (medical and psychological) as part of clinical treatment for the study. Study procedures including consent were reviewed by the UK Health Research Authority.

Data sharing. These are highly sensitive data from a small group of vulnerable young people treated in a single service and the risk of identification and disclosure is high. Research ethics permissions at the time the study was undertaken did not include permission to share data. After discussions with the Health Research Authority, UK, an anonymised dataset modified to remove sensitive data and minimise disclosure risk of personal information has been deposited with the UK Data Service.

Results

Participants received psychosocial assessment and support within the GIDS before entering the study for a median of 2.0 years (IQR 1.4 to 3.2; range 0.7 to 6.6). The median time between first medical assessment at UCLH and starting treatment was 3.9 months (IQR 3.0 to 8.4; range 1.6 to 25.7). Median time in the study was 31 months (IQR 20 to 42, range 12 to 59).

Baseline characteristics of the participants by birth-registered sex are shown in Table 1. Median age at consent was 13.6 years (IQR 12.8 to 14.6, range 12.0 to 15.3). A total of 25 (57%) were birth-registered as male and 19 (43%) as female. At study entry, birth-registered males

Table 1. Participant characteristics at baseline.

		Total sample	Birth-registered sex	
		n = 44	male	female
			n = 25	n = 19
Age at consent (years)	Median (IQR)	13.6 (12.8, 14.6)	13.4 (12.7, 14.1)	13.9 (13.5, 14.7)
Ethnic group n (%)	white	39 (89)	24 (96)	15 (79)
	South Asian	1 (2)	1 (4)	0
	black	2 (5)	0	2 (11)
	Mixed ethnicity	2 (5)	0	2 (11)
Pubertal status n (%)	Stage 2	0	0	0
	Stage 3	19 (43)	17 (68)	2 (10)
	Stage 4	16 (36)	5 (20)	11 (58)
	Stage 5	9 (21)	3 (12)	6 (32)
Menarcheal status n (%)	Premenarcheal	-	-	4 (21)
	Post-menarcheal	-	-	15 (79)
Time in study (months)	Median (IQR)	31 (20, 42)	37 (24, 43)	29 (17, 36)
Age at end of pathway (years)	Median (IQR)	16.1 (16.0, 16.4)	16.1 (16.0, 16.5)	16.1 (16.0, 16.3)

At baseline, all participants had normal endocrinology, karyotype, imaging and clinical phenotype on physical examination for birth-registered sex and normal full blood count and liver and renal function. No participants had evidence of disorders of sexual differentiation. Eight participants (18%) had vitamin D insufficiency at baseline and were given vitamin D supplements.

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were predominantly in stage 3 puberty (68%) whilst birth-registered females were predominantly in stages 4 (58%) or 5 (32%) with 79% (15/19) post-menarcheal. 89% of participants were of white ethnicity. Birth-registered females were on average 6 months older than birth-registered males at study entry.

Response to treatment

All participants achieved adequate suppression of gonadotropins and sex hormones by 6 months (mean LH 0.5IU/L; mean FSH 1.4IU/L) and maintained it throughout the study (see Table 2). Liver function, basic haematology and biochemistry were normal in all participants at 3–6 months. All post-menarcheal birth-registered females reported amenorrhoea in the 3 months after starting GnRHa treatment and remained so throughout treatment. No participants reported progression in pubertal development. Height and weight were normal at baseline. Height growth continued through the study but more slowly than expected for age, thus

Table 2. Growth and gonadotropin levels at baseline, 12, 24 and 36 months.

Growth		Baseline		12 months		24 months		36 months	
		n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Height	z-score	44	0.4 (0.1, 0.7)	44	0.2 (-0.1, 0.4)	24	0.0 (-0.4, 0.4)	14	0.0 (-0.5, 0.5)
Weight	z-score	44	0.8 (0.4, 1.3)	44	0.8 (0.3, 1.3)	24	0.6 (-0.1 1.3)	14	1.0 (0.1, 1.9)
BMI	z-score	44	0.7 (0.2, 1.1)	44	0.7 (0.2, 1.2)	24	0.6 (-0.1, 1.3)	14	1.1 (0.3, 1.9)
Gonadotropins									
LH	IU/L	42*	4.2 (2.8, 5.6)	44	0.60 (0.42, 0.68)	17	0.40 (0.22, 0.60)	7	0.30 (0.14, 0.46)
FSH	IU/L	42*	3.9 (3.2, 4.5)	44	1.3 (1.0, 1.7)	17	1.0 (0.6, 1.5)	7	1.4 (0.7, 2.2)

*In two participants data recorded as normal at baseline were not available.

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height z-score fell over time (Table 2). Weight and BMI z-scores were stable from baseline to 24 months but increased at 36 months.

Three participants had brief periods off GnRHa prior to their 16th birthday. In one, treatment was withdrawn by clinicians due to non-attendance at clinics and restarted 4 months later. Another requested a period off GnRHa to think further about treatment in view of other things happening in their life; they restarted 4 months later. A third, birth-registered male, stopped GnRHa for 9 months to attempt to store sperm, contrary to their earlier decision not to, and restarted afterwards.

Median age at the end of the GnRHa pathway was 16.1 years (Table 1). A quarter of participants made their decision more than six months later, either because they wished to delay due to school exams or other events or because clinicians felt they were not yet ready to make the decision. One young person decided to stop GnRHa and not start cross-sex hormones, due to continued uncertainty and some concerns about side-effects of cross-sex hormones. The remaining 43 (98%) elected to start cross-sex hormones.

Bone mineral density. BMD was available on 44 participants at baseline, 43 at 12 months, 24 at 24 months and 12 at 36 months (Table 3). Numbers were lower for hip than for spine as some hip scans were not done for technical reasons. The table shows mean values at baseline and 12, 24 and 36 months, along with mean baseline values corresponding to the paired samples at each time point. There was no change from baseline in spine or hip at 12 months nor in hip at 24 and 36 months, but at 24 months lumbar spine BMC and BMD were higher than at baseline, as was lumbar BMC at 36 months. Lumbar and hip BMD age-adjusted z-scores were in the normal range at baseline but point-estimates fell at 12 and 24 months but not at 36 months. Point-estimates for height-adjusted z-scores for lumbar and hip BMD also fell at 12 and 24 months but not at 36 months.

Psychological outcomes. For the standardised questionnaires, baseline assessments were conducted at a median of 0.5 (IQR 0.4, 0.8) years before starting treatment, and were available for all 44 participants by self-report and 43 by parental report. Data on the CBCL, YSR, Kidscreen-52, BIS and CGAS were normally distributed whilst those for UGDS and the CBCL and YSR self-harm indices were skewed.

The first psychological follow-up was at a median of 13 (IQR 12, 14) months after start of treatment, with ASEBA data available for 41 participants (parent and self-report). ASEBA data at 24 months (median 25 (21, 28)) were available on 20 young people by parent report and 15 by self-report, and at 36 months (median 36 (29, 39)) on 11 by parent report and 6 by self-report.

Formal testing was undertaken only for key ASEBA outcomes (Table 4). For the CBCL total t-scores, there was no change from baseline to 12, 24 or 36 months. Similarly for the YSR total t-score, there was no change from baseline to 12 or 24 months; YSR data at 36 months (n = 6) were not analysed. There were no significant changes in parent-report CBCL self-harm index scores from baseline to 12, 24 or 36 months, nor for self-report YSR self-harm index scores.

Other psychological outcomes are described in Table 5. Point-estimates of scores on the Kidscreen-52, BIS, UGDS and CGAS showed little change over time."

The pre-specified outcomes of BMD at lumbar spine, YSR total t-score and CGAS score at 12 months, adjusted separately for birth-registered sex and baseline pubertal status, along with the baseline level of the outcome, are shown in Table 6. None of the outcomes were associated with birth-registered sex or pubertal status, and there were no important interactions.

Participant experience, satisfaction and side effects. 41 participants completed interviews at 6–15 months (median 9) and 29 at 15–24 months (median 21); 3 missed both. Fig 1 shows proportions with positive or negative changes for life overall, mood and friendships, with summary data for all questions shown in S1 Appendix (S1 and S2 Tables).

Table 3. Bone mineral density outcomes at baseline, 12, 24 and 36 months.

				12 months					24 months				
		Baseline			Baseline for those followed up	Follow-up	Change	p		Baseline for those followed up	Follow-up	Change	p
		n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Lumbar	BMC	44	39.5 (35.9, 43.1)	42	39.6 (35.8, 43.4)	41.2 (38.2, 44.2)	1.6 (0.2, 3.1)	0.03	24	34.1 (30.3, 37.9)	40.1 (36.7, 43.5)	6.0 (4.0, 7.9)	<0.0001
	BMD	44	0.76 (0.71, 0.80)	43	0.76 (0.71, 0.80)	0.77 (0.72, 0.81)	0.01 (-0.00, 0.03)	0.17	24	0.68 (0.63, 0.74)	0.73 (0.68, 0.78)	0.05 (0.03, 0.07)	0.0001
Hip	BMC	43	25.2 (23.2, 27.1)	39	25.5 (23.4, 27.6)	26.1 (24.4, 27.9)	0.7 (-0.2, 1.5)	0.13	22	23.9 (21.2, 26.6)	26.3 (24.1, 28.6)	2.4 (0.7, 4.1)	0.008
	BMD	43	0.80 (0.75, 0.86)	39	0.81 (0.75, 0.87)	0.82 (0.78, 0.86)	0.01 (-0.02, 0.05)	0.6	22	0.76 (0.68, 0.85)	0.79 (0.74, 0.84)	0.03 (-0.04, 0.10)	0.4
BMD z-scores	Spine	44	-0.3 (-0.7, 0.0)	43	-0.3 (-0.7, 0.1)	-1.0 (-1.3, -0.7)			24	-0.5 (-1.1, 0.0)	-1.5 (-2.1, -0.8)		
	HAZ spine	44	-0.5(-0.8, -0.1)	43	-0.4 (-0.8, -0.1)	-1.0 (-1.3, -0.6)			24	-0.7 (-1.2, -0.1)	-1.3 (-1.9, -0.7)		
	Hip	43	-0.5 (-0.9, -0.1)	39	-0.5 (-0.9, -0.1)	-1.0 (-1.3, -0.6)			21	-0.5 (-1.1, 0.1)	-1.4 (-2.0, -0.9)		
	HAZ hip	43	-0.7 (-1.0, -0.3)	39	-0.6 (-1.0, -0.2)	-0.9 (-1.3, -0.5)			21	-0.5 (-1.1, 0.1)	-1.2 (-1.7, -0.6)		
				36 months									
					Baseline for those followed up	Follow-up	Change	p					
				n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)						
Lumbar	BMC			12	37.05 (31.0, 43.1)	42.4 (37.4, 47.4)	5.3 (2.8, 7.8)	0.0007					
	BMD			12	0.72 (0.65, 0.80)	0.76 (0.70, 0.82)	0.03 (.00, 0.07)	0.05					
Hip	BMC			12	26.1 (22.1, 30.0)	26.8 (21.2, 32.3)	0.7 (-3.8, 5.2)	0.7					
	BMD			12	(0.82, 0.73, 0.91)	0.81 (0.74, 0.88)	-0.009 (-0.05, 0.03)	0.6					
BMD z-scores	Spine			12	-0.2 (-1.0, 0.6)	-1.5 (-2.2, -0.8)							
	HAZ spine			12	-0.4 (-1.2, 0.3)	-1.3 (-2.2, -0.5)							
	Hip			12	-0.3 (-1.3, 0.6)	-1.1 (-1.8, -0.5)							
	HAZ hip			12	-0.5 (-1.5, 0.5)	-1.0 (-1.8, -0.2)							

BMD: bone mineral density; BMC bone mineral content; HAZ height adjusted z-score.

BMD z-scores were not formally tested–see Methods.

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Most participants reported positive or a mix of positive-negative changes in their life at both time points. At 6–15 months 46% reported only positive changes, including feeling happier, relieved, less facial hair or stopping periods. A further 37% reported both positive and negative changes such as feeling happier but also experiencing hot flushes and headaches. In addition 12% reported overall negative changes namely hot flushes, tiredness, and feeling more emotional, while 5% reported no change. At 15–24 months, 55% reported solely positive changes such as feeling happier, no longer experiencing side effects and feeling more

Table 4. ASEBA outcomes at baseline, 12, 24 and 36 months.

				12 months					24 months				
			Baseline		Baseline for those followed up	Follow-up	Change	p		Baseline for those followed up	Follow-up	Change	p
		n	mean (95% CI)	n	mean (95% CI)	mean (95% CI)	mean (95% CI)		n	mean (95% CI)	mean (95% CI)	mean (95% CI)	
Parent report CBCL	Total problems t-score	43	61.6(58.4, 64.7)	41	61.5(58.2, 64.7)	61.8(58.4, 65.1)	0.3(-2.0, 2.6)	0.8	20	61.2(56.5, 65.8)	60.2(54.6, 65.8)	-1.0(-4.0, 2.1)	0.5
	Externalising problems t-score	43	55.8(52.4, 59.3)	41	55.7(52.1, 59.3)	55.4(51.8, 59.0)			20	55.4(49.9, 60.9)	55.2(48.9, 61.5)		
	Internalising problems t-score	43	62.1(58.7, 65.5)	41	61.8(58.3, 65.3)	62.9(59.5, 66.3)			20	60.4(55.7, 65.1)	60.1(54.6, 65.6)		
Self-report YSR	Total problems t-score	44	57.9(55.0, 60.8)	41	57.6(54.5, 60.6)	58.4(54.6, 62.2)	0.8(-3.1, 4.8)	0.7	15	55.1(50.9, 59.2)	56.5(50.6, 62.5)	1.5(-3.4, 6.3)	0.5
	Total problems z-score (ref: Netherlands)	44	1.01(0.67, 1.36)	41	0.97(0.62, 1.33)	0.99(0.55, 1.42)			15	0.66(0.17,1.15)	0.65(-0.05, 1.36)		
	Total problems z-score (ref: Australia)	44	0.72(0.37, 1.06)	41	0.68(0.32, 1.03)	0.68(0.24, 1.12)			15	0.39(-0.11,0.89)	0.37(-0.32, 1.07)		
	Externalising problems t-score	44	52.3(49.2, 55.5)	41	52.3(49.2, 55.4)	52.5(48.7, 56.3)			15	53.1(48.5, 57.6)	52.3(45.3, 59.4)		
	Internalising problems t-score	44	58.0(54.9, 61.2)	41	57.7(54.3, 61.0)	60.1(55.9, 64.3)			15	53.9(49.9, 58.0)	55.9(50.8, 61.1)		
Self-harm scores													
Parent report CBCL	Median (IQR)	43	0(0, 1)	40	0(0, 1)	0(0, 1)		0.3	20	0(0, 1)	0(0, 1)		>0.9
Self-report YSR	Median (IQR)	43	0(0, 1)	39	0(0, 1)	0(0, 2)		0.4	15	0(0, 0)	0(0, 0)		0.3
				36 months									
					Baseline for those followed up	Follow-up	Change	**p**					
				n	mean (95% CI)	mean (95% CI)	mean (95% CI)						
Parent report CBCL	Total problems t-score			11	62.4(55.1, 69.6)	61.1(52.3, 69.9)	-1.3(-6.6, 4.0)	0.6					
	Externalising problems t-score			11	56.8(48.0, 65.6)	56.2(48.3, 64.1)							
	Internalising problems t-score			11	60.4(53.5, 67.2)	62.5(53.6, 71.5)							
Self-harm scores													
Parent report CBCL	Median (IQR)			11	0(0, 1)	0(0, 1)		0.8					

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comfortable with puberty suspended. A further 17% reported both positive and negative changes including less body hair but continued growth in height, or having clearer skin but also experiencing more hunger, weight gain and tiredness. 17% reported largely negative changes such as mood swings, tiredness and hot flushes whilst 10% reported no change.

Reports of change in mood were mixed. At 6–15 months, the majority reported mood to be improved (49%), mixed changes (such as both feeling happier but experiencing some mood swings; 15%) or no change (7%), however 24% reported negative changes in mood such as

Table 5. Other psychological outcomes at baseline, 12, 24 and 36 months.

		Baseline		12 months		24 months		36 months	
		n	mean (95% CI)	n	mean (95% CI)	n	mean (95% CI)	n	mean (95% CI)
Kidscreen-52 HRQOL									
Parent report CBCL t-scores	Physical wellbeing	42	44.9(41.4, 48.5)	36	40.4(37.5, 43.3)	14	40.5(36.8, 44.2)		
	Psychological Wellbeing	41	39.8(36.7, 42.8)	36	39.0(35.4, 42.6)	14	42.4(36.9, 48)		
	Moods and Emotions	41	40.6(37.6, 43.6)	36	41.2(37.3, 45.1)	14	42.5(36.3, 48.7)		
	Self-perception	42	34.6(32.6, 36.5)	36	34.8(32.0, 37.5)	14	34.8(31.3, 38.2)		
	Autonomy	42	46.2(43.2, 49.2)	36	48.2(45.0, 51.4)	14	46.7(41, 52.4)		
	Parent relations and home life	42	48.1(44.5, 51.6)	35	46.7(42.9, 50.5)	14	49.5(44.1, 54.9)		
	Social support and peers	39	48.0(44.7, 51.4)	36	51.9(48.4, 55.3)	13	51.4(45.6, 57.2)		
	School environment	42	38.2(35.0, 41.4)	35	39.4(35.3, 43.4)	13	43.7(36, 51.3)		
	Social acceptance	39	44.7(40.7, 48.7)	32	42.3(38.1, 46.4)	13	43.5(35.9, 51.2)		
	Financial resources	42	37.9(33.9, 41.9)	36	35.8(31.5, 40.2)	14	36.3(26.4, 46.3)		
Self-report t-scores	Physical wellbeing	42	45.1(41.8, 48.5)	36	41.5(38.0, 45.0)	13	43.9(38.9, 48.9)		
	Psychological Wellbeing	42	43.0(39.6, 46.4)	36	41.1(37.0, 45.2)	14	51(45.8, 56.2)		
	Moods and Emotions	42	46.3(42.7, 49.9)	36	43.9(40.4, 47.3)	14	50.1(45.5, 54.7)		
	Self-perception	42	38.8(36.7, 40.9)	36	37.9(35.1, 40.6)	14	43.1(39.9, 46.2)		
	Autonomy	42	46.6(43.6, 49.6)	36	46.7(42.9, 50.5)	13	51.9(47.4, 56.4)		
	Parent relations and home life	42	49.7(46.2, 53.2)	36	48.7(45.2, 52.3)	14	58.4(53.3, 63.5)		
	Social support and peers	37	45.6(42.5, 48.7)	35	48.1(44.6, 51.6)	14	49.7(44.3,55.1)		
	School environment	41	45.9(42.3, 49.4)	36	44.7(39.7, 49.7)	14	49(43.6, 54.3)		
	Social acceptance	41	47.4(43.5, 51.3)	33	45.5(40.9, 50.1)	13	53.6(46.3, 60.8)		
	Financial resources	42	42.2(38.1, 46.3)	34	43.2(38.2, 48.1)	14	46.3(39.1, 53.5)		
Body image scale	Overall score	42	3.1(2.8, 3.3)	40	3.2(3.0, 3.4)	16	3(2.7, 3.2)	8	3.1(2.4, 3.7)
	Primary characteristics score	42	4.5(4.2, 4.7)	39	4.3(4.2, 4.5)	16	4.5(4.3, 4.7)	8	4.2(3.9, 4.5)
	Secondary characteristics score	41	2.9(2.6, 3.1)	40	3(2.8, 3.3)	16	2.9(2.5, 3.2)	8	2.9(2, 3.8)
	Neutral characteristics score	42	2.5(2.203, 2.707)	40	2.7(2.5, 3.0)	-	-		
Utrecht Gender dysphoria score	Median (IQR)	41	4.8(4.6, 5.0)	40	4.7(4.6, 5.0)	18	4.7(4.3, 5.0)		
Clinical outcome									
CGAS global score	Mean (95% CI)	42	62.9(59.6, 66.2)	35	64.1(59.9, 68.3)	18	65.7(59.6, 71.8)	12	66.0(58.1, 73.9)

Note: Change in outcomes in this Table were not formally tested.

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Table 6. Associations between birth-registered sex and baseline pubertal status and outcomes at 12 months.

		Outcomes at 12 months adjusted for baseline								
		BMD at lumbar spine			YSR total t-score			GCAS score		
		n	Coefficient (95% CI)	p	n	Coefficient (95% CI)	p	n	Coefficient (95% CI)	p
Birth-registered sex										
Main effect (baseline value of outcome)		43	0.86 (0.75, 0.97)	<0.0001	41	0.43 (0.05, 0.82)	0.03	33	0.74 (0.42, 1.06)	<0.0001
Birth-registered sex	Male (ref)		0			0			0	
	Female		-0.02 (-0.05, 0.01)	0.2		2.1 (-5.2, 9.4)	0.6		-3.2 (-10.0, 3.5)	0.3
Pubertal status										
Main effect (baseline value of outcome)		43	0.85 (0.72, 0.97)	<0.0001	41	0.43 (0.01, 0.84)	0.04	33	0.69 (0.37, 1.00)	<0.0001
Pubertal stage at baseline	3		0.008 (-0.03, 0.04)	0.7		0.2 (-8.3, 8.7)	0.9		1.6 (-5.5, 8.8)	0.6
	4 (ref)		0			0			0	
	5		-0.009 (-0.05, 0.03)	0.7		0.4 (-9.9, 10.8)	0.9		-7.9 (-17.6, 1.8)	0.11

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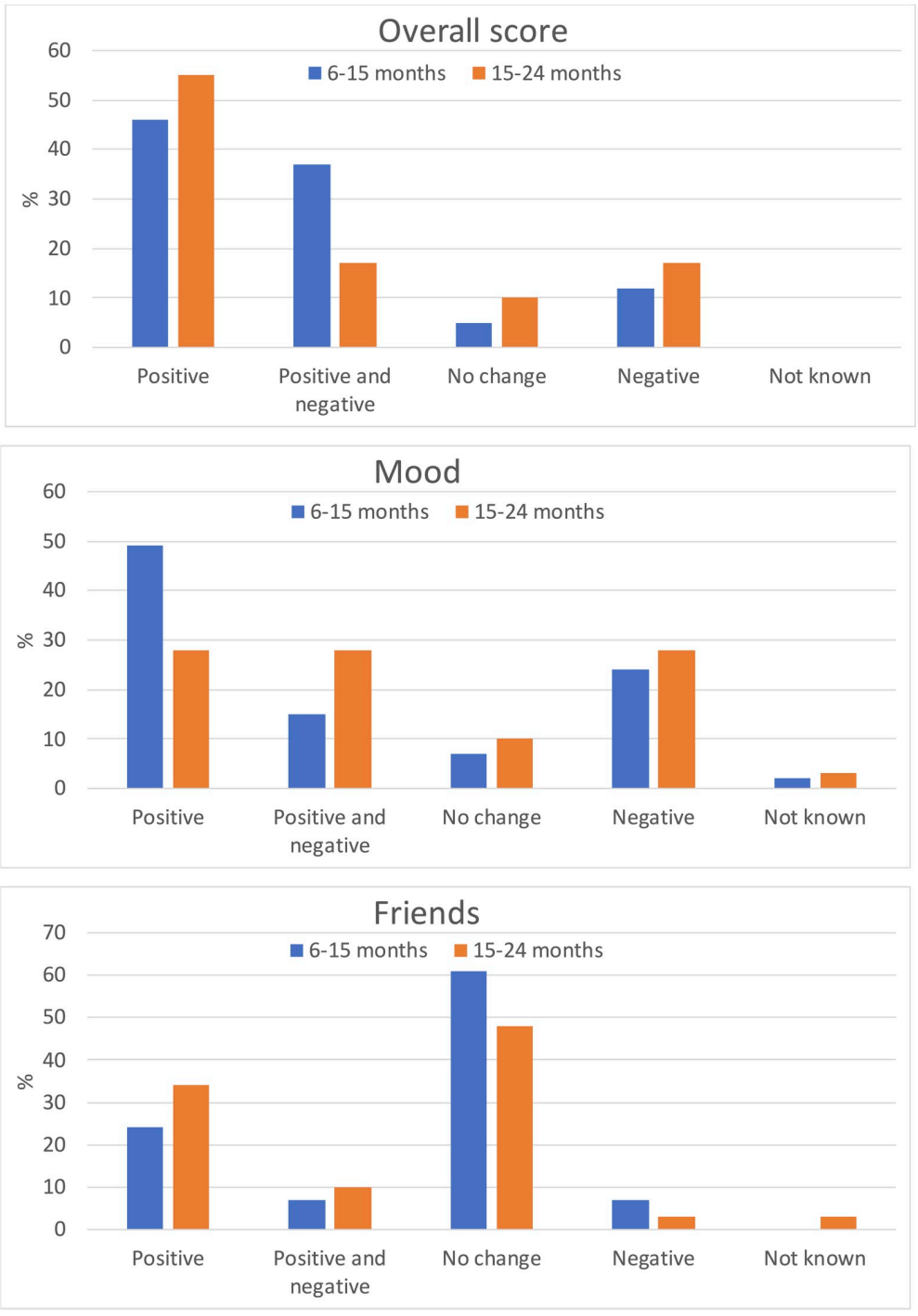

Fig 1. Ratings of change in life overall, mood and friendships at 6–15 months (n = 41) and 15–24 months (n = 29).

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experiencing more mood swings or feeling low. Findings at 15–24 months were similar. The most common negative change was reduced energy levels, reported by 29% at 6-15m and 38% at 15-24m.

Young people's reports of change in family and peer relationships were predominantly positive or neutral at both time points. Positive changes included feeling closer to the family,

Table 7. Adverse events reported across the study.

Participants	0-6m	7-12m	13-24m	25+m
	n = 44	n = 44	n = 36	n = 24
	n (%)	*n (%)*	*n (%)*	*n (%)*
Mild headaches or hot flushes	11 (25%)	10 (23%)	8 (22%)	4 (17%)
Moderate or severe headaches and hot flushes	2 (5%)	4 (9%)	1 (3%)	0
Fatigue—mild	2 (5%)	3 (7%)	3 (8%)	1 (4%)
Fatigue–moderate or severe	0	0	0	0
Mood swings	1 (2%)	0	0	0
Weight gain	1 (2%)	0	1 (3%)	0
Sleep problems	1 (2%)	0	1 (3%)	0
Other events	0	0	0	0
Total events recorded*	18	17	14	5

* individuals may have more than 1 event.

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feeling more accepted and having fewer arguments. Those reporting both positive and negative change reported feeling closer to some family members but not others. At 6–15 months, negative family changes were largely from family members not accepting their trans status or having more arguments. But by 15–24 months only one young person reported this. Improved relationships with peers related to feeling more sociable or confident and widening their circle of friends; negative changes related to bullying or disagreements at school. Again, at 15–24 months only one young person reported negative change, related to feelings of not trusting friends.

At 6–15 months, changes in gender role were reported by 66% as positive, including feeling more feminine/masculine, living in their preferred gender identity in more (or all) areas of life and feeling more secure in their gender identity, with no negative change reported. At 15–24 months, most reported no change although 41% reported positive changes including experimenting more with physical appearance and changing their details on legal documents.

All young people affirmed at each interview that they wished to continue with GnRHa treatment. Note that this was also the case when asked routinely at medical clinics (excepting those who briefly ceased GnRHa as noted above).

Adverse events. Adverse events are shown in Table 7. All adverse events were minor and anticipated, i.e. they were previously described in study participant information and/or noted in the triptorelin medication package inserts. Anticipated adverse events were common in the first two years, particularly mild headaches or hot flushes which were reported in 25% at 0-6m, 23% at 7-12m and 22% at 13-24m. Moderate or severe headaches and/or hot flushes were uncommon. Birth-registered females with distressing headaches or hot flushes were offered 'add-back' oestrogen therapy, and two accepted treatment briefly with very small doses of oestradiol, which was effective in reducing symptoms. Mild fatigue was reported by 5–8% over the first two years and no participants reported moderate or severe fatigue. Sleep problems, mood swings and weight gain were reported by very small numbers and in each case symptoms were mild. Adverse events were less common after 12 months of treatment.

Discussion

We report the short and medium-term outcomes of a prospective cohort of 44 young people with persistent and severe GD treated with GnRHa resulting in pubertal suppression from mid-puberty for 1–4 years. Young people were considered for recruitment after lengthy

assessment, spending an average of 2 years and up to 6 years within the GIDS psychological service before being referred to the endocrine clinic for assessment to enter the study. Medical assessment found no endocrine abnormalities at baseline. GnRHa treatment started in the majority of participants in later stages of puberty, with 57% in puberty stages 4 and 5 and 79% of birth-registered females being post-menarcheal. After starting GnRHa all quickly achieved and maintained suppression of pubertal hormones and none experienced pubertal progression. At the end of the study, 43 (98%) chose to start cross-sex hormones whilst one young person chose to stop GnRHa and continue with puberty consistent with their birth-registered sex.

As anticipated, pubertal suppression reduced growth that was dependent on puberty hormones, i.e. height and BMD. Height growth continued for those not yet at final height, but more slowly than for their peers so height z-score fell. Similarly for bone strength, BMD and BMC increased in the lumbar spine indicating greater bone strength, but more slowly than in peers so BMD z-score fell. These anticipated changes had been discussed with all participants before recruitment to the study. Young people experienced little change in mean weight or BMI z-score in the first two years. The rise in weight and BMI z-score at 36 months may represent a trend towards greater adiposity in those on GnRHa for a prolonged period, or reflect a higher baseline in this group.

Information on side-effects was available through routine reporting in medical clinics and in the participant experience interviews. Anticipated side effects of treatment were common, particularly mild symptoms directly related to suppression of sex hormones. Severe symptoms were uncommon. Fatigue or low energy was reported rarely in medical clinic assessments but frequently at interview (38% at 15-24m). The relationship of symptoms such as headaches, fatigue and sleep disturbance to GnRHa treatment is unclear as they are all very common in early adolescence [36,37], although a conservative perspective would regard them as side-effects of treatment.

Young people experienced little change in psychological functioning across the study. We found no differences between baseline and later outcomes for overall psychological distress as rated by parents and young people, nor for self-harm. Outcomes that were not formally tested also showed little change.

Participant experience of treatment as reported in interviews was positive for the majority, particularly relating to feeling happier, feeling more comfortable, better relationships with family and peers and positive changes in gender role. Smaller numbers reported having mixed positive and negative changes. A minority (12% at 6–15 months and 17% at 15–24 months) reported only negative changes, which were largely related to anticipated side effects. None wanted to stop treatment due to side effects or negative changes. We are not aware of comparative patient experience data from other cohorts.

The median age at consent in our study was very similar to that in the earliest published outcome study of mid-pubertal suppression using GnRHa treatment in Dutch young people (13.6 years) [24]. Similarly to this Dutch cohort, all but one of our participants elected to start cross-sex hormones after completing the GnRHa pathway. However they spent an average of 31 months on GnRHa compared with 23 months in the Dutch cohort [24]. In our study, the successful suppression of puberty and cessation of menses with GnRHa, the impact on height growth [4,16,38] and BMD [4,16] and the normality of liver and renal function through treatment were each consistent with previous reports [4,16].

Our findings that BMD increased over time in the lumbar spine but more slowly than in same age peers, resulting in a fall in z-score, are similar to others [4,14,39,40]. The fall in height-adjusted BMD z-score was consistent with but larger than the fall in height z-score. We found that birth-registered sex and pubertal status at baseline were not associated with later BMD. There is evidence that accretion of bone mass resumes and that BMD increases with the

start of cross-sex hormone therapy [4,14,39,41]. Future research needs to examine longer-term change in BMD in young people treated with mid-pubertal suppression.

We reported a range of adverse events previously described to be associated with pubertal suppression [42], with the exception of mild sleep disturbance although this is a known association with triptorelin use. As anticipated, the withdrawal of sex hormones produces symptoms such as headaches and lack of energy, although in the great majority (11 of 13 at 0–6 months; 10 of 14 at 7–12 months; 8 of 9 at 13–24 months) the symptoms were minor. Symptoms diminished over time as has previously been noted [4], and no young people chose to cease treatment due to the side-effects.

Our finding that 1 participant ceased pubertal suppression and did not commence cross-sex hormones is somewhat similar to the experience of one US cohort and a second Dutch cohort; Kuper et al. described that 2 of approximately 57 young people aged 10–15 years who commenced pubertal suppression treatment stopped this treatment without commencing cross-sex hormones [17]. Brik et al. reported that in a cohort of 137 young people who began GnRHa between 10 and 18 years and were followed until eligible to commence cross-sex hormones, 5 (3.6%) ceased treatment and did not later commence cross-sex hormones [19].

Three longitudinal studies from the Netherlands and the USA have examined psychological function over time in cohorts of young people treated with GnRHa and then cross-sex hormones [17,18,24], although the two US cohorts were of limited size. Our study adopted the same psychological outcome measures as the Dutch cohort, to facilitate comparison [24]. Mean baseline YSR scores in our cohort were similar to those previously reported in 141 young people aged 12–18 years from the London GIDS [43], and baseline CBCL and YSR scores were close to those at baseline from the original Dutch cohort [24]. A number of other studies have shown that young people with GD have higher scores on the CBCL or YSR than same-age population peers, and that they are similar to young people referred to clinical services for a range of mental health problems [44–46]. Population-based studies in America support higher baseline levels of mental health problems amongst young people with GD, with the prevalence of self-harm notably higher than for male or female peers [47,48]. Young people in our study had baseline YSR scores 0.7–1.0 SD higher than norms for age in comparable countries [29,46].

We found no evidence of change in psychological function with GnRHa treatment as indicated by parent report (CBCL) or self-report (YSR) of overall problems, internalising or externalising problems or self-harm. This is in contrast to the Dutch study which reported improved psychological function across total problems, externalising and internalising scores for both CBCL and YSR and small improvements in CGAS [24]. It also contrasts with a previous study from the UK GIDS of change in psychological function with GnRHa treatment in 101 older adolescents with GD (beginning $>$ 15.5 years) which reported moderate improvements in CGAS score over 12 months of GnRHa treatment [49]. CGAS scores in this previous study increased from 61 to 67 with GnRHa treatment, similar to those (63 at baseline, 66 at 24 months) in our study. Follow-up of the Kuper et al. cohort found non-significant changes in depression and anxiety scores in those (n = 25) who had only pubertal suppression treatment, although improvements were seen in the whole sample combining these with those receiving cross-sex hormones [17]. A second US cohort reported that in 23 young people who had received pubertal suppression (using GnRHa or anti-androgens in birth-registered males and either GnRHa or medroxyprogesterone in birth-registered females), there was a reduction in depression scores in birth-registered males but not females.

A recent large US survey found that those who received pubertal suppression in early or mid adolescence had lower odds of lifetime suicidal ideation when studied in adulthood compared with those who did not, regardless of whether they later received cross-sex hormones

and after adjustment for a range of confounding factors [50]. This implies an enduring benefit of pubertal suppression on psychological function, however the cross-sectional design and retrospective exposure classification means the findings require replication. Data are also available from other conditions in which GnRHa is used to suppress puberty during adolescence. A trial of GnRHa suppression of puberty during early adolescence in young people born small-for-gestational-age (SGA) who were also treated with human growth hormone (GH) reported that those treated with GnRHa had similar cognitive and psychological function in adult life to those treated only with GH [51].

The differences between our findings and the previous GIDS study re change in psychological function may relate simply to sample size. But why our findings differ from those of the Dutch study is unclear. They may relate to the timing of assessments; we assessed young people multiple times whereas in the Dutch study the second assessment was shortly before starting cross-sex hormone treatment. Alternatively, there may have been baseline differences in the two cohorts. Whilst some aspects of psychological function were similar, as noted above, the baseline CGAS scores were notably higher in the Dutch group (indicating better function). A previous international comparison study has found that young people aged 12–18 years with GD from the UK have higher scores indicating greater problems on the CBCL and YSR than those from the Netherlands, Belgium and Switzerland [52].

Psychological distress and self-harm are known to increase across early adolescence. Normative data show rising YSR total problems scores with age from age 11 to 16 years in non-clinical samples from a range of countries [29]. Self-harm rates in the general population in the UK and elsewhere increase markedly with age from early to mid-adolescence, being very low in 10 year olds and peaking around age 16–17 years [53–56]. Our finding that psychological function and self-harm did not change significantly during the study is consistent with two main alternative explanations. The first is that there was no change, and that GnRHa treatment brought no measurable benefit nor harm to psychological function in these young people with GD. This is consonant with the action of GnRHa, which only stops further pubertal development and does not change the body to be more congruent with a young person's gender identity. The second possibility is that the lack of change in an outcome that normally worsens in early adolescence may reflect a beneficial change in trajectory for that outcome, i.e. that GnRHa treatment reduced this normative worsening of problems. In the absence of a control group, we cannot distinguish between these possibilities. We aimed to use normative reference data to examine this issue. However age- and gender-standardised t-scores for ASEBA and other outcomes cannot answer this question as they cover a very broad age range (e.g. 12–18 years). We had anticipated that z-scores on the YSR available by calendar year for two comparable countries (Netherlands; Australia) might be informative however confidence intervals were too wide to draw reliable inferences.

Gender dysphoria and body image changed little across the study. This is consistent with some previous reports [24] and was anticipated, given that GnRHa does not change the body in the desired direction, but only temporarily prevents further masculinization or feminization. Other studies suggest that changes in body image or satisfaction in GD are largely confined to gender affirming treatments such as cross-sex hormones or surgery [57]. We found that birth-registered sex and baseline pubertal status were not associated with later psychological functioning on GnRHa, consistent with previous reports [24,49].

These data correct reports from a recent letter by Biggs [58] which used preliminary data from our study which were uncleaned and incomplete data used for internal reporting. In addition there were many statistical comparisons which inflated the risk of type 1 error. Our statistical analysis plan restricted testing all outcomes for differences by sex due to the type 1

error risk. Contrary to Biggs's letter, we found no evidence of reductions over time in any psychological outcomes, and no material differences by sex.

Strengths and limitations

Our study provides comprehensive data on this cohort during follow-up, with an anonymised dataset containing standardised scores deposited to allow other researchers to replicate our findings where data-sharing allows. The study size and uncontrolled design were key limitations. The small sample size limited our ability to identify small changes in outcomes. This was an uncontrolled observational study and thus cannot infer causality. Further, many of the outcomes studied here, including psychological function, self-harm and BMD, undergo normative changes by age and developmental stage during puberty that could confound any observed effect of GnRHa treatment in an uncontrolled study. The analysis plan aimed to take these issues into account as far as possible, however this particularly limits the potential for the study to show benefits or harms from treatment. However, some conclusions can be drawn. It is unlikely that the reported adverse events such as headaches do not relate directly to GnRHa treatment. Equally, given that there were no changes in psychological function and differences in point estimates were minimal for nearly all outcomes, it is unlikely that the treatment resulted in psychological harm. Observational studies are important sources of data on harms of treatment [59–61].

Our data are subject to a number of other limitations. This was an unfunded study undertaken within a clinical service and we were dependent on the clinical service for data collection. There were varying sample sizes for differing tests as some participants did not attend certain investigations and some follow-up medical tests were processed locally to patients; these data are reported as normal or otherwise. Missing items on psychological questionnaires resulted in some unusable data. Some young people found repeated completion of questionnaires about gender issues intrusive and refused to complete them at later follow-ups, as has been reported in other studies [62]. This questionnaire fatigue also affected parent responses. Scoring of psychological questionnaire data was rechecked at the completion of the study however this was not possible in very small numbers of participants in whom only scale scores rather than individual item data were preserved during data migration in hospital clinical information systems. In sensitivity analyses, repeat analysis of ASEBA psychological outcomes restricted to those with rescored data showed highly similar findings to the full sample (see S3 Table in S1 Appendix).

A more detailed qualitative evaluation of participant experience was not possible due to lack of interviewer time, and reporting of interview data was restricted to perceptions of positive or negative change and the giving of examples.

Implications and conclusions

Treatment of young people with persistent and severe GD aged 12–15 years with GnRHa was efficacious in suppressing pubertal progression. Anticipated effects of withdrawal of sex hormones on symptoms were common and there were no unexpected adverse events. BMD increased with treatment in the lumbar spine and was stable at the hip, and BMD z-score fell consistent with delay of puberty. Overall participant experience of changes on GnRHa treatment was positive. We identified no changes in psychological function, quality of life or degree of gender dysphoria.

The great majority of this cohort went on to start cross-sex hormones, as was hypothesized given the severity and continuation of their GD. However one young person did not, providing some evidence that development of gender identity continues on GnRHa treatment and

confirming the importance of continuing supportive psychological therapy to allow further exploration of gender identity and a range of future pathways whilst on GnRHa.

This cohort will be followed up longer term to examine physical and mental health outcomes into early adulthood. However larger and longer-term prospective studies using a range of designs are needed to more fully quantify the harms and benefits of pubertal suppression in GD and better understand factors influencing outcomes [3]. These are beginning to be funded in a number of countries [63].(https://logicstudy.uk) Given that pubertal suppression may be both a treatment in its own right and also an intermediate step in a longer treatment pathway, it is essential for such studies to examine benefits and harms across the longer pathway including pubertal suppression and initiation of cross-sex hormones.

Supporting information

S1 Appendix.
(DOCX)

S2 Appendix. Statistical analysis plan.
(DOCX)

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