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Ethical dilemmas and decision-making in the healthcare for transgender minors

Vrouenraets, L.J.J.J.

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Use of fertility preservation among a cohort of transgirls in the Netherlands

Tessa Brik

Lieke J. J. J. Vrouwenraets

Sebastian E. E. Schagen

Andreas Meissner

Martine C. de Vries

Sabine E. Hannema

ABSTRACT

Purpose: The primary aims of the study are to examine the rate of attempted fertility preservation (FP) among a Dutch cohort of transgirls who started treatment with gonadotropin-releasing hormone analogues (GnRHa) and the reasons why adolescents did or did not choose to attempt FP.

Methods: The study was a single-centre retrospective review of medical records of 35 transgirls who started treatment with GnRHa between 2011 and 2017.

Results: Ninety-one percent of adolescents were counselled on the option of FP. Thirty-eight percent of counselled adolescents attempted FP, and 75% of them were able to cryopreserve sperm suitable for intrauterine insemination (IUI) or intracytoplasmic sperm injection (ICSI). Younger and Caucasian transgirls were less likely to attempt FP. No specific reason for declining FP was known in 33% adolescents, 32% of adolescents were not able to produce a semen sample because of early puberty, 17% felt uncomfortable with masturbation, 17% did not want to have children, and 13% wanted to adopt.

Conclusions: One third of adolescents attempted FP, which is much more than the percentage reported in previous studies from the United States. One third of the transgirls could not make use of FP because they were unable to produce a semen sample because of early pubertal stage. For these adolescents, alternatives need to be explored.

INTRODUCTION

Many transgender adolescents wish to undergo gender-affirming medical treatment (GAMT), which may initially consist of puberty suppression (PS) with gonadotropin-releasing hormone analogues (GnRHa), followed by gender-affirming hormones (GAH) and, in adulthood, gender-affirming surgery (Coleman et al., 2012; Hembree et al., 2017). Whereas the effects of GnRHa are reversible, long-term use of gender-affirming sex steroids may affect fertility, and if gonadectomy is performed, the transgender person will definitely be infertile (de Roo et al., 2016; Hembree et al., 2017; Olson, Forbes, & Belzer, 2011). Infertility may have a major impact on the lives of transgender minors. Previous studies showed that concerns about (future) fertility are associated with a significant reduction in quality of life (Carter et al., 2010; Trent et al., 2003; Wenzel et al., 2005). Research among adult transmen described significantly better self-perceived mental health status and vitality among those with children than those without children (Wierckx et al., 2012). This suggests that fertility preservation (FP) can influence quality of life in transgender adolescents.

A previous study showed that most transgender adolescents wanted to have children in the future (Strang et al., 2018). Another study, however, pointed out that transgender minors more often state “never wanting to have children” than has been reported in cisgender persons (Nahata, Tishelman, Caltabellotta, & Quinn, 2017). A survey revealed that 62% of adult transmen wanted to have children, and about 38% would have considered FP if it had been available at the time (Wierckx et al., 2012). Fifty-one percent of adult transwomen would have considered sperm cryopreservation if it had been offered (de Sutter, Verschoor, Hotimsky, & Kira, 2002). Nowadays, the World Professional Association for Transgender Health and Endocrine Society recommend counselling regarding FP options before initiating treatment with GnRHa (Coleman et al., 2012; Hembree et al., 2017). However, two recent studies from the United States indicate that transgender minors rarely use FP (Chen, Simons, Johnson, Lockart, & Finlayson, 2017; Nahata et al., 2017).

We aimed to investigate how many adolescents made use of FP in a Dutch cohort of transgirls who started treatment with GnRHa. In addition, we assessed if information about the risk of infertility had been given, if discussion of the option of FP was documented in the medical file, and what the given reason for declining FP was if the adolescent had not made use of FP. Furthermore, we explored what factors were associated with the use of FP.

METHODS

Study population

Transgirls who were referred to start treatment with GnRHa between June 2011 and August 2017 at the gender identity clinic Curium-Leiden University Medical Centre were eligible. Those who declined participation were excluded. The study population consisted of 35 transgirls. Before the start of treatment with GnRHa, all adolescents had a diagnostic evaluation to confirm the diagnosis gender dysphoria according to the DSM-5 criteria (Hembree et al., 2017) and to assess the presence of any psychiatric or psychosocial problems that might interfere with treatment. This evaluation included an IQ test and a psychiatric interview. Written informed consent for treatment with GnRHa was obtained from adolescents and for those aged younger than 16 years also from their parents/guardians. Informed consent forms contained information about the risk of infertility. The option of FP was discussed by the paediatric endocrinologist. If adolescents wished to cryopreserve sperm and thought they would be able to produce a semen sample via masturbation, they were referred to a fertility clinic where semen samples were preserved, on three occasions if indicated.

Data collection

Extracted data from the medical files were age, IQ, Tanner stage, testicular volume, ethnicity, sexual orientation, psychiatric comorbidity (depression, anxiety disorder, posttraumatic stress disorder, and autism spectrum disorder), family situation (i.e., raised in an intact family, divorced parents or other [including adopted, living in a foster-home]) and information about the desire to have children.

Ethics

The study is part of an observational study on the effects of hormonal treatment in adolescents with gender dysphoria, which was approved by the medical ethical committee of the Leiden University Medical Centre.

Statistics

Statistical analyses were performed with SPSS version 23 (IBM) using the t-test for continuous variables or Mann-Whitney U test if data were not normally distributed. Chi-square test or Fisher's exact test was used for categorical variables. No Bonferroni correction was applied when testing the association between several variables and the use of FP because this was meant to explore rather than confirm factors that may be of influence.

RESULTS

Study population characteristics are summarized in table 10.

Table 10. Characteristics of the 35 transgirls at the start of treatment with gonadotropin-releasing hormone analogues

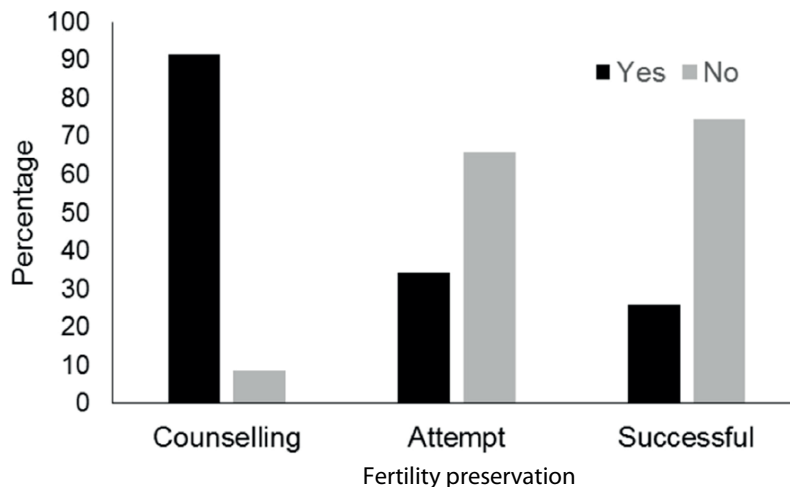
Characteristics	Mean \pm SD, median (range), or number (%)
Age (years)	14.8 \pm 1.9
IQ total	100 \pm 17
Testicular volume (mL)	15 \pm 6
Tanner genital stage	5 (2-5)
Ethnicity (<i>n</i> = 35)	
Caucasian	25 (71)
Other	10 (29)
Attracted to (<i>n</i> = 30)	
Men only	22 (63)
Other	8 (23)
Psychiatric comorbidity (<i>n</i> = 34)	
Yes	16 (46)
No	18 (51)
Interested in having children (<i>n</i> = 15)	
Yes	7 (20)
No	4 (11)
Maybe	4 (11)

Missing data are not shown.

SD refers to standard deviation.

All adolescents had been informed on the risk of infertility, and 91% (*n* = 32) had been counselled about the option of FP. In the other three cases, it was not clear from the medical notes if they had been counselled; two of them were early pubertal (testicular volume 5 mL) so that no FP options were actually available. Forty-one percent (*n* = 13) of the counselled transgirls were referred for sperm cryopreservation, and 38% (*n* = 12) had actually been to the fertility clinic to try to cryopreserve sperm (figure 4). One transgirl who had been referred had not been to the fertility clinic and had not started treatment with GnRH α yet at the time of the analysis because of psychosocial issues.

Figure 4. Counselling about fertility preservation, attempted fertility preservation, and successful fertility preservation (sperm suitable for IUI or ICSI preserved) among 35 transgirls

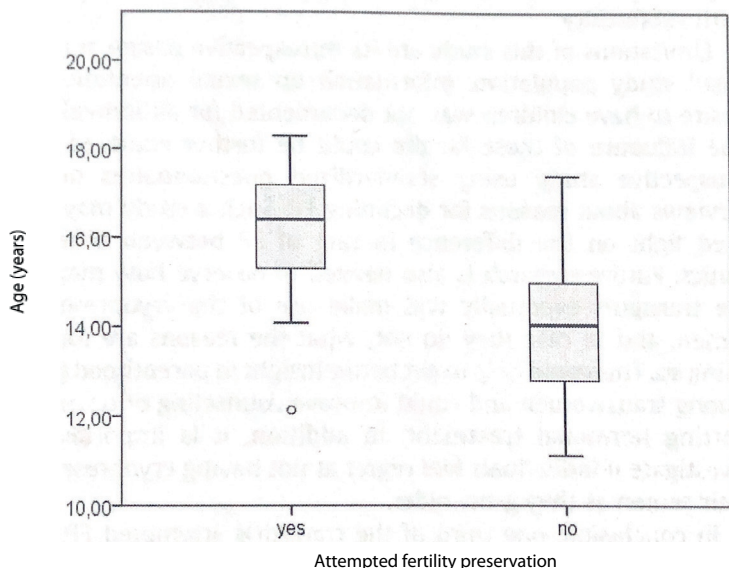


ICSI refers to intracytoplasmic sperm injection; IUI refers to intrauterine insemination.

Given reasons for not wanting to be referred for FP were (some of the transgirls gave more than one reason) not wanting to have children (17%, $n = 4$), wanting to adopt (13%, $n = 3$, one specifically said she did not want to have children who would be like her), feeling uncomfortable with masturbation or having an aversion of their penis (17%, $n = 4$), and feeling uncomfortable with the idea of being the biological father of the child (4%, $n = 1$). Eight persons (33%) did not give a specific reason for declining FP. Eight adolescents (33%) were not referred for FP because they were in early puberty and were not able to produce a semen sample through masturbation.

The mean age at the start of treatment with GnRHa in the group of transgirls who attempted FP was significantly higher (age 16.1 years \pm 1.7) than in the group that did not attempt FP (age 14.2 years \pm 1.7; $p = .003$; figure 5). Tanner stage and testicular volume were also higher in the group who attempted FP (Tanner stage G5, range 4-5; testicular volume 17.2 mL vs. G4, range 2-5; 13.4 mL), but these differences were not significant. The mean IQ in this population was 100 \pm 17. The mean IQ in the group who attempted FP was not significantly different from that in the group who did not (respectively 94 \pm 15 vs. 103 \pm 18; $p = .17$).

Figure 5. Age at the start of treatment with gonadotropin-releasing hormone analogues in transgirls who did and did not attempt fertility preservation. Mean age was significantly lower in the group who did not attempt ($n = 23$) than in the group who did attempt fertility preservation ($n = 12$, $p = .003$)



Because options to have children may depend on the sex of future partners, we investigated if sexual orientation was related to the use of FP. Transgirls who did not attempt FP were as likely to be attracted to men only (12 of 19) as transgirls who did attempt FP (10 of 11; $p = .2$), but only two transgirls were not attracted to men at all. No significant differences were seen in family situation (living together with both parents vs. separated parents/foster parents/adopted or other) between the two groups. However, fewer Caucasian girls attempted FP than girls with other ethnicities including Asian, African, and South American (20% vs. 70%; $p = .02$). Forty-seven percent of the transgirls suffered from psychiatric comorbidity (depression, anxiety disorder, posttraumatic stress disorder, or autism spectrum disorder). Those with psychiatric comorbidity were as likely to attempt FP as those without. Information about the desire to have children was present in medical files of 43% of the transgirls. All four transgirls who stated not wanting to have children declined FP, whereas 36% of those who were (potentially) interested in having children attempted FP.

Of the 12 adolescents who attempted FP, one was unable to ejaculate. She was 12 years old and at Tanner stage G4, with testicular volume 15 mL. One post-pubertal adolescent had azoospermia, whereas another had severe oligozoospermia with a few viable spermatozoa after thawing in only one sample, considered marginally usable for intracytoplasmic sperm

injection (ICSI) in the future, and no sperm was found when testicular sperm extraction was performed. The other nine adolescents, aged 14.1-18.5 years, one at Tanner stage G4, the others at Tanner stage G5, with testicular volume 15-25 mL, stored semen that was of sufficient quality to be used for intrauterine insemination ($n = 5$) or ICSI ($n = 4$).

DISCUSSION

This study shows that many transgirls have an interest in FP indicating this is an important topic to discuss before starting treatment with GnRHa. Tools are being developed to facilitate such discussions. Strang and colleagues (2018) have developed a Transgender Youth Fertility Attitudes Questionnaire, and Johnson and colleagues (2016) have indicated that they aim to develop a modular decision aid.

Most studies of FP by adolescents have been performed among cancer patients at risk for infertility and have shown that many decline FP because they do not want to delay the cancer treatment and because of severe illness and possibly costs (Burns, Boudreau, & Panepinto, 2006; Klosky et al., 2009). Two studies among transgender adolescents have also shown low uptake of FP (9%-14%) (Chen et al., 2017; Nahata et al., 2017). The use of FP in the present study is higher although still lower than the 51% of adult transgender women who stated that they would have made use of FP if it had been available (de Sutter et al., 2002). Thus, it will be important to see whether some of the transgirls who declined FP will regret their decision later in life. In the study of Strang and colleagues (2018), about half of 25 transgender adolescents who completed a questionnaire about fertility attitudes indicated they felt that their feelings about wanting biological children might change when they were older. On the other hand, to our knowledge, there are no data available yet on the actual use of cryopreserved semen by transgender adults apart from a report of one individual who used her cryopreserved semen for donor insemination of her partner (Wierckx et al., 2012).

The percentage of transgirls who did not wish to have children is similar to that reported by others (12%-37%) (Chen et al., 2018; Nahata et al., 2017; Strang et al., 2018). Previous studies in cisgender men showed a correlation between having a desire to have children and rate of sperm banking (Pacey et al., 2013). Such a correlation was not found in the present study, but in 57% of the medical files, information about the desire to have children was missing. In previous studies, more transgender adolescents stated they were interested in adopting children than in the present study, which raises the question if there might be a different view on adoption among adolescents in the United States compared with the Netherlands (Chen et al., 2018; Nahata et al., 2017).

Early pubertal phase precluded FP for a number of transgirls. Adolescents and physicians are faced with this dilemma between the wish for early treatment to avoid virilization on the one hand, and the wish for FP on the other hand, more often now that increasing numbers of adolescents are referred for hormonal treatment at younger ages. Research on *in vitro* maturation of spermatozoa might provide future solutions for these early pubertal adolescents (Wallace, Blough, & Kondapalli, 2014).

The need to masturbate was another reason to decline FP. Alternative options for extracting sperm such as testicular sperm extraction or electroejaculation stimulation could be used to facilitate FP. In the case report and literature review by Lau, Li and Soh (2014), electroejaculation appeared to be relatively safe. However, in the Netherlands, this procedure is currently only offered by some clinics to adolescents starting cancer treatment when it can be combined with a procedure that already requires anaesthesia such as placement of a central venous catheter.

Differences in costs of the procedure and health insurance coverage may explain some of the difference in use of FP between studies. Although costs were mentioned as a barrier by only 5% of transgirls in the retrospective study by Nahata and colleagues (2017), the reason for refusal of FP was unknown in 26%; therefore, costs may have been an important factor for more adolescents. In the present study, none of the patients had mentioned costs as a reason to decline FP probably because most insurance will cover most of the costs of FP.

When thinking of pregnancy/conception options, transgirls attracted to women might be more likely to cryopreserve their sperm than those attracted to men because this would allow them to conceive a child with their female partner. A previous study did indeed find that lesbian or bisexual transwomen were more likely to state that they would, if possible, have cryopreserved sperm than asexual or heterosexual transwomen (de Sutter et al., 2002). However, we did not find such a correlation, but this may have been because of the small group size and missing data, as only four transgirls stated they were attracted to women. Furthermore, sexual orientation is difficult to assess with certainty at a young age, so these results need to be interpreted with caution. In addition, transgirls who are attracted to men may also wish to use FP to allow them to have children with the help of a surrogate mother. Surrogacy (if not commercial) is legal in the Netherlands.

Caucasian transgirls were more likely to decline FP than adolescents with other ethnicities, but the latter were older than Caucasian transgirls (15.9 ± 1.5 years vs. 14.4 ± 1.9 years), so this association may be confounded by age. On the other hand, there may be a true association with ethnicity because of the differences in reproductive pressure and importance given to reproduction in different cultures. This is supported by a study by Schmid, Kirchengast, Vytiska-Binstorfer, and Huber (2004) where cisgender infertile women

from Islamic countries felt more distress because of infertility than Caucasian women. A survey among transgender adolescents also found that minors of colour expressed an interest in having biological children more often than white non-Hispanic/Latino minors (Chen et al., 2018). It is uncertain to what extent other relevant issues identified in previous studies, such as stigma towards sexual and gender minority parenting and pressure from one's family to have biological children or the feeling of disappointing one's family by not having biological children played a role in the population included in the present study (Chen et al., 2018; Strang et al., 2018).

Because of the lack of a control group, it is not possible to compare the outcome of FP among the transgirls to that in cis-gender adolescent males. In adults, poorer semen parameters and a higher incidence of oligozoospermia have been observed in transwomen compared with cisgender controls (Hamada et al., 2015; Li, Rodriguez, Gabrielsen, Centola, & Tanrikut, 2018). The cause of this difference is unclear, but psychological stress, self-induced high scrotal position of the testes, the use of tight underwear, and undisclosed hormone use were suggested as possible explanations as well as genetic causes (Hamada et al., 2015). Some of the adolescents in the present study also 'tucked away' their testes which may affect testicular function. One adolescent with severe oligozoospermia had one inguinal testis, which can be associated with subfertility.

Limitations of this study are its retrospective design and the small study population. Information on sexual orientation or desire to have children was not documented for all individuals. The influence of these factors could be further explored in a prospective study using standardized questionnaires or interviews about reasons for declining FP. Such a study may also shed light on the difference in rate of FP between different clinics. Future research is also needed to observe how many of the transgirls eventually will make use of the cryopreserved semen, and in case they do not, what the reasons are for not doing so. This could help to get better insight in parenthood goals among transwomen and could improve counselling of transgirls starting hormonal treatment. In addition, it is important to investigate if individuals feel regret at not having cryopreserved their semen as they grow older.

In conclusion, one third of the transgirls attempted FP, and most were able to store sperm suitable for future intrauterine insemination or ICSI. This stresses the need to discuss this topic before the start of treatment with GnRHa. Making different sperm extraction options available such as testicular sperm extraction or electroejaculation stimulation may make FP more accessible for transgirls for whom masturbation is a barrier. FP is currently not available for early pubertal adolescents, but research in this area might open up FP options for this group too. With future options on the way, an ethical and legal debate is essential, taking into account the right to equality and non-discrimination and the right to procreate of transgender people.

