Sperm quality in transgender women before or after gender affirming hormone therapy—A prospective cohort study

Kenny A. Rodriguez-Wallberg1,2 | Jakob Häljestig2 | Stefan Arver3 | Anna L. V. Johansson4 | Frida E. Lundberg1,4

1Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden
2Department of Reproductive Medicine, Division of Gynecology and Reproduction, Karolinska, University Hospital, Stockholm, Sweden
3Department of Medicine/Huddinge, Karolinska Institutet and ANOVA Andrology, Sexual Medicine, Trans Medicine Karolinska University Hospital, Stockholm, Sweden
4Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Correspondence
Kenny A. Rodriguez-Wallberg, Department of Reproductive Medicine, Division of Gynecology and Reproduction, Karolinska University Hospital, 141 86 Stockholm, Sweden. Email: kenny.rodriguez-wallberg@ki.se

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Abstract
Background: Due to recent changes in the legal framework, access to fertility preservation (FP) for transgender individuals has opened up in several countries. In Sweden and the Nordic countries, fertility preservation for medical reasons is fully reimbursed as part of the established tax-funded healthcare services. As this issue is relatively new, procedures for FP have seldom been reported in the transgender patient population. The very limited literature has indicated that transgender women may have poorer sperm quality than cisgender men when assessing samples aimed at semen banking.

Objectives: To assess sperm quality parameters of semen samples provided for FP by transgender women before or after gender affirming hormone therapy (GAHT), and to compare sperm quality with a reference population of unscreened men defined by the World Health Organization (WHO). Additionally, we aimed to describe referral patterns over calendar time and estimate time from referral to semen cryopreservation.

Material and Methods: Prospective cohort study of 212 transgender women referred for FP to the Reproductive Medicine Clinic of Karolinska University Hospital, Sweden, between 2013 and 2018. Among 177 individuals that provided semen samples for cryopreservation, 16 had previously received GAHT.

Results: Individuals with previous GAHT presented with significantly lower total sperm count than individuals without GAHT (p = 0.002). However, higher proportions of sperm abnormalities were also noted among individuals who had not undergone previous GAHT, compared to the WHO reference population (p < 0.001). Referrals of transgender women for FP increased over time. The median time from referral to semen cryopreservation was 27 days.

Conclusions: A high occurrence of sperm abnormalities was found in transgender women, especially among individuals who had previously received GAHT. The results underline the importance of thoroughly discussing parenthood options and FP with patients early after diagnosis and referring the patients for semen banking preferably before starting GAHT.

Study Registration: ClinicalTrials.gov NCT04602962

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1 | INTRODUCTION

In 2013, the previous requirement of sterilization for change of legal gender was abolished in the Swedish legislation.1 Hence, transgender individuals may now be included in clinical programs of fertility preservation (FP), a healthcare that is publicly tax funded in Sweden and offered to the whole population.2 The term transgenderism signifies an incongruence between individuals’ assigned sex at birth and their self-perceived gender identity, as opposed to cisgender individuals for whom the gender identity matches the assigned sex at birth.3 Because of recent improvements in public awareness, and acceptance, the known transgender population has grown. Studies from the US and Europe have reported that between 0.4% and 1.1% of the population experience gender incongruence.4-9 A Swedish cohort study recently estimated that 2.3% of adults “felt like someone of a different sex,” 2.8% “would like to live as or be treated as someone of a different sex” and that 0.5% wanted to undergo gender affirming therapy.7

The feeling of gender incongruence may be combined with psychological distress called gender dysphoria that often prompts the person to seek medical care.8 Before undergoing gender affirming therapy, a thorough investigation by a multi-professional team including psychiatrists, psychologists, endocrinologists, and social workers, is needed to verify that the gender dysphoria is caused by transgenderism and to identify and manage additional co-morbidities. Gender affirming therapy encompasses a series of interventions such as endocrine therapy, voice therapy, hair removal, and plastic surgery. Pre-pubertal patients may receive suppressing hormone therapy to postpone pubertal development, which gives time for the diagnostic work-up and enables delayed entry into the preferred pubertal development at around 16 years of age. The gender affirming hormone therapy (GAHT) for transgender women most often consists of estrogen combined with continued suppression of testicular activity with or without peripheral androgen receptor blockade.9 This treatment has a known negative effect on the patient’s fertility since the testicles usually atrophy with a significant drop of testosterone secretion, causing sperm production to halt.10,11 Gender affirming surgery for transgender women includes orchiectomy, which causes irreversible sterility.9

Because of the negative effect of GAHT on future fertility, it is important to discuss the possibility of FP before starting gender affirming therapy.11,12 FP for transgender women is most often performed through cryopreservation of sperm from ejaculated semen, although other methods have been described.13 The proportion of transgender women that would opt for freezing their semen has been estimated to 51% in a previous European study from 2002.14 However, several studies have reported that less than 10% of transgender women utilized FP, some citing high cost and delay of GAHT as potential barriers to FP.15-17

Semen analysis is the single most important tool for assessing sperm quality with a sensitivity of 89.6% for detecting problems that may cause infertility.18 Few studies have investigated the sperm quality of transgender women.19-23 In three of these studies, transgender women who had begun GAHT prior to FP were excluded because of its known negative effect on the sperm quality,19-21 while one study reported lower sperm quality in transgender women undergoing GAHT.22 However, the studies on transgender women who had not started GAHT also reported poorer semen parameters compared to cisgender men.19-23 Although the reasons for this are unclear, hypotheses include physiological issues with spermatogenesis, psychological stress, androgen receptor polymorphism, genetic disorders and transgender specific factors such as intentional retraction of the testes into the groin (i.e., tucking), wearing of tight underwear to conceal the genitalia and unrepeated self-medication with GAHT.19,20

This study aimed to investigate the semen parameters of transgender women that undergo FP before or after starting GAHT and to compare the parameters to a reference population of men from the general population defined by the World Health Organization (WHO). The secondary aims were to estimate the proportion of transgender women desiring FP and to estimate the time from referral to semen sampling for cryopreservation in our healthcare system.

2 | MATERIAL AND METHODS

2.1 | Study design and study population

The study cohort included patients assigned male at birth with a gender dysphoric diagnosis (transsexualism, ICD-10 F64.0, other gender identity disorders, F64.8, or unspecified gender identity disorder, F64.9) during reproductive age, and who were referred for cryopreservation of semen aiming at FP at Karolinska University Hospital, Section of Reproductive Medicine, in Stockholm, Sweden between June 2013 and October 2018. This center provides FP within the tax-funded healthcare system for the whole Healthcare Region of Stockholm, approximately 2 million inhabitants. The referrals were submitted by psychiatrists, andrologists, or endocrinologists involved in the gender identity team of the hospital, usually at the time when the diagnosis was confirmed. Individuals that wished to provide semen samples for cryopreservation were instructed to have a period of abstinence of 3–5 days before providing an ejaculate. Samples were obtained by masturbation. Semen parameters were analyzed at the Reproductive Medicine clinic at Karolinska University Hospital,
which is an accredited laboratory for analysis of sperm samples for infertility work-up and fertility treatments. Data on semen parameters including volume, total sperm count, sperm concentration, and sperm motility were extracted from the clinical registry of the Reproductive Medicine clinic (Linnéfiler®). Information on date of referral, date of FP, age, date of GAHT initiation and discontinuation, and type of GAHT was collected from the hospital electronic records (TakeCare®). Sperm abnormalities were defined as values below the 5th percentile of a reference population of men with unknown fertility, assumed to be representative of the general population, as described by the WHO.24

To obtain the total number of patients of assigned male sex at birth that received a diagnosis of gender dysphoria within specialist out-patient care between June 2013 and October 2018 in the Healthcare Region of Stockholm, data were obtained from the Swedish Patient Register at the National Board of Health and Welfare, Sweden.25 These data provided an estimation of the eligible population from which the study cohort was sampled. Using the personal identification number assigned to all Swedish residents, individuals with male sex assigned at birth were identified with the 9th (sex specific) digit.

The study was performed in accordance with the Declaration of Helsinki and the Regional Ethics Committee in Stockholm approved the study (Dnr 2011/1758-31/2, amendments 2014/470-32, 2014/1360-32, 2014/1825-32, 2018/275-32 and 2018/1453-32).

2.2 | Statistical analysis

Sperm parameters (volume, concentration, count, and motility) were summarized as medians and interquartile ranges. For patients with multiple samples, the mean value of all samples was used for each sperm parameter. Firstly, the sperm parameters were compared as continuous variables for transgender women with and without previous GAHT using the Wilcoxon rank-sum test. Secondly, sperm abnormalities were compared as binary variables for transgender women with and without previous GAHT and the reference population described by the WHO.24 The proportions of sperm abnormalities among transgender women with and without previous GAHT were compared to the reference population using Fisher’s exact test. A double-sided \( p < 0.05 \) was considered statistically significant. Statistical analyses were performed using Stata (StataCorp. 2019. Stata Statistical Software: Release 16: StataCorp LLC).

3 | RESULTS

In total, 212 transgender women were referred to Karolinska University Hospital for cryopreservation of semen aiming at FP between June 1st 2013 and October 31st 2018 (Figure 1). After excluding 33 patients who did not proceed to FP and 2 who could not produce a semen sample, the final cohort included 177 transgender women. Nearly all individuals (\( n = 169 \)) had received the diagnosis transsexualism (ICD-10: F64.0), while six patients had received a diagnosis of other or unspecified gender identity disorder (F64.8 or F64.9). The median age at FP was 24, ranging from 14 to 54 (Table 1). The median time from referral to first cryopreservation of semen was 27 days. In total, 16 transgender women (9%) had started GAHT prior to FP, whereof 6 had used only estrogen and 10 had used estrogen in combination with an anti-androgen. The duration of GAHT ranged from 6 to 66 months (0.5–5.5 years) and the time from discontinuation of GAHT to first FP attempt ranged from 1 to 5 months.
3.1 | Sperm quality analyses

Sperm parameters were compared between transgender women who had received GAHT previously or not prior to provision of the semen samples for FP (Table 2). Sperm motility did not have a valid value in one case, which was excluded. The median values for all sperm parameters were lower among transgender women who had received GAHT before FP compared to no GAHT, with statistically significant differences in sperm concentration \((p = 0.011)\) and total sperm count \((p = 0.002)\).

The frequencies of sperm abnormalities compared to the WHO reference group are presented in Table 3. There was no significant difference in the proportion of transgender women with low semen volume compared to the reference population. However, low total sperm count, low sperm concentration, and poor sperm motility were significantly more common in transgender women both before and after GAHT than in the reference population \((p < 0.001\) for all comparisons). The distribution of sperm parameters in transgender women and in the WHO reference population of men of unknown fertility status are shown as box and whiskers plots in Figure 2.

3.2 | Trends of fertility preservation over time

There was an overall increase of transgender women referred for FP between 2013 and 2018 (Figure 3). The number of FP referrals increased by 60% per year on average, despite a reduced number of referrals during 2017. Over time, the proportion of referred patients who actually went on to cryopreserve sperm at the clinic increased from 56% in 2013 to 91% in 2018.

The total number of individuals with male sex assigned at birth that received a diagnosis of gender dysphoria in the Stockholm region during the study period according to the Swedish Patient Register at the National Board of Health and Welfare are presented in Table 4. During the years 2013 to 2018, a total of 1417 individuals between the ages 10 and 54 received a diagnosis of gender dysphoria. A minority of these patients were referred for FP. FP was more common in individuals of younger ages, ranging from 16% of diagnosed individuals aged 10–19 to 2% in individuals aged 40–54. The number of individuals receiving a diagnosis of gender dysphoria has continuously increased every year, while the proportion who got referred for FP has shown some variation ranging between 5 and 17% in the years 2013 to 2018. In total, 11% of all individuals of young reproductive age receiving a diagnosis of gender dysphoria were referred for FP and 9% actually attended the fertility clinic to bank semen samples aiming at FP.

4 | DISCUSSION

As the transgender population that approach medical care in connection with gender dysphoria is growing, there is an increasing need for research aiming to improve transgender health care. This prospective cohort study aimed to evaluate the sperm quality of transgender women undergoing FP and the trends of FP among transgender women since its legalization in 2013. High frequencies of sperm abnormalities were found in the study population and sperm quality was significantly lower in individuals that had begun GAHT prior to FP, specifically total sperm count and sperm concentration. Although there has been an increasing number of transgender women presenting for FP between 2013 and 2018, most individuals are still very young and the utilization rate of FP to cryopreserve semen still remains low among transgender women in our cohort.

4.1 | Sperm quality

Significantly lower total sperm counts and sperm concentration were found in individuals previously undergoing GAHT. This finding was anticipated since GAHT has previously been shown to have a negative impact on spermatogenesis. Adeleye et al published a cohort study in 2018 which found that sperm quality was significantly lower in 7 transgender women currently using GAHT, but not in 3 transgender women who had previously used GAHT, when compared to 18 never users. In a cohort study by de Nie et al, 2020, sperm abnormalities were not significantly more common in 12 transgender women who had previously used GAHT than in 248 never users. These differences may partly be explained by variations in time since GAHT discontinuation, although interpretations are limited by the small numbers of transgender women exposed to GAHT.

| Table 2 Comparison of semen parameters in patients with or without GAHT prior to FP |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Semen parameter                | Patients without previous GAHT \(n = 161\) | Patients with previous GAHT \(n = 16\) | \(p\)-value* |
| Semen volume (ml)              | Median (IQR)    | Median (IQR)    | 0.172           |
| 3.2 (2.2–4.2)                  | 2.7 (1.9–3.4)   | 0.172           |
| Sperm concentration \((x10^6) /ml\) | 28.0 (9.0–58.0) | 3.7 (0–43.0)   | 0.011           |
| Total sperm count \((x10^6)\)  | 79.3 (24.7–189.0) | 12.3 (0–79.6) | 0.002           |
| Sperm motility (%)**           | 58.0 (46.7–67.0) | 34.1 (25.0–63.5) | 0.055           |

Abbreviations: FP, fertility preservation; GAHT, gender affirming hormone therapy; IQR, interquartile range.
*\(p\)-values calculated using the Wilcoxon rank-sum test.
**Calculated only from samples containing sperm, 150 patients without previous GAHT and 10 with previous GAHT.
When comparing to a reference population of men with unknown fertility status, transgender women were found to have significantly higher frequencies of sperm abnormalities both before and after GAHT. This supports the findings of Hamada et al, 2015, Li et al, 2018, and de Nie et al, 2020, who suggested that transgender women may have poorer sperm quality than cisgender men.19,20,23 It is known that suppression of testicular function by estrogens, GnRH analogs or progestogens with antiandrogenic activity such as cyproterone acetate may induce spermatogenesis arrest and that the recovery period may vary considerably between individuals.26,27 At present, there is not a standardized screening protocol to improve the chances to obtaining sperms in semen samples provided by transgender women that have received GAHT. Serum determinations of gonadotropin secretion (FSH and LH), testosterone, and inhibin could be useful to monitor time for clearance of depot preparations, such as GnRHa or estrogens, if those have suppressed testicular function. There is also a need to investigate the role of other factors that may impair sperm quality, such as testes retraction or compression, and to establish and evaluate pharmacological treatment protocols that could improve the chance of recovery of spermatogenesis after GAHT in transgender women.19,20

### 4.2 | Trends over time

Since the legalization of FP for transgender individuals in 2013 there has been an increase in referrals of transgender patients to the Section of Reproductive Medicine for semen banking. This is in accordance with the growing population of known transgender individuals in Stockholm as well as worldwide.28-30 The increase in referral rates appears fairly steady in this report apart from a drop in 2017 to about half of what might have been expected. We could not identify any apparent reason for the drop. Although there has been an increase in FP, it is still a minority of individuals with a gender dysphoric diagnosis who get referred. This may be partially explained by the findings of Nahata et al, that many transgender individuals were planning on adopting children rather than using their own gametes and some did not desire to have children.14 Furthermore, all

### TABLE 3 Frequency of sperm abnormalities compared to the WHO reference population

| Sperm abnormality                       | Reference population (n = 930) | Patients without previous GAHT (n = 161) | p-value* | Patients with previous GAHT (n = 16) | p-value* |
|-----------------------------------------|-------------------------------|----------------------------------------|----------|--------------------------------------|----------|
| Low semen volume (<1.2 ml)             | 46/929 (5.0%)                 | 7/161 (4.4%)                           | 0.845    | 1/16 (6.3%)                          | 0.561    |
| Low sperm concentration (<9 × 10⁹/ml)  | 47/930 (5.0%)                 | 39/161 (24.2%)                         | <0.001   | 10/16 (62.5%)                        | <0.001   |
| Low total sperm count (<20 × 10⁹)      | 46/928 (5.0%)                 | 35/161 (21.7%)                         | <0.001   | 8/16 (50.0%)                         | <0.001   |
| Low sperm motility** (<36%)             | 46/928 (5.0%)                 | 24/150 (16.0%)                         | <0.001   | 5/10 (50.0%)                         | <0.001   |

Abbreviations: GAHT, gender affirming hormone therapy; WHO, World Health Organization.
* p-values calculated using Fisher’s exact test compared to reference population.
**Calculated only from samples containing sperm.

FIGURE 2  Semen parameters in transgender women with and without previous GAHT and WHO reference population. The boxes represent the quartiles and the lines within them are the medians; the whiskers extend from the 10th to the 90th centiles and the dots represent the 5th and 95th centiles. WHO ref, World Health Organisation reference population of unscreened men; TW, transgender women; GAHT, gender-affirming hormone therapy.
individuals who receive a gender dysphoric diagnosis may not want to undergo gender affirming treatment and will therefore not need FP. Åhs et al showed, in a study of the population of Stockholm, that 2.3% felt like someone of a different sex but only 0.5% of the population wanted gender affirming treatment.7

4.3 | Number of days from referral to fertility preservation

The time transgender patients need to wait for FP determines the length of time they have to wait for GAHT. Being unable to tolerate this waiting causes some patients to start GAHT before FP or turn down the option of FP entirely.16 This study shows that in the Stockholm region, transgender women could plan an appointment at the Reproductive Medicine laboratory to give their first semen samples for FP within 1 month from receiving a diagnosis of transgenderism.

4.4 | Strengths and limitations

The strength of this study is the large sample size with a total of 177 individuals included of whom 161 had not started GAHT prior to FP, all belonging to a large healthcare region with established referral routines and public healthcare available to all individuals. This is one of the largest studies to date reporting sperm quality in transgender women accessing FP. Furthermore, the tax-funded public healthcare available in Sweden allows the access to FP regardless of socioeconomic status, a barrier recognized in several studies from other countries.31 A limitation of this study is the lack of a control group of cisgender men from the same geographical region and time period, which would have enabled more reliable estimates of impaired sperm quality in transgender women. However, a well-described WHO reference population was used as an external control group, which enables comparisons with other studies using this reference. The sperm quality in this population may have been impaired by medical issues as well as non-medical gender-affirming behaviors such as tucking. Since this information was not available, it was not possible to further investigate the reasons for the poorer sperm quality seen in the study population. The study also lacked information on body mass index and smoking habits, factors which may have been associated with sperm quality.

4.5 | Significance

This study adds evidence and confirms the findings of the previous literature on an impaired sperm quality in transgender women, although for reasons still unknown and not only dependent on use of GAHT.19,20 Individuals who had previously undergone GAHT had a more marked impairment of sperm quality, which differed significantly from that of transgender women with no GAHT. Therefore, it is important that FP is thoroughly discussed before planning for GAHT treatment.22 Furthermore, we could observe an increasing trend in transgender women presenting for FP since legalization,
were significantly lower sperm counts and sperm concentration and motility in transgender women who underwent FP. This study showed low sperm counts and hampered sperm movement indicative of higher demands to fertility clinics. The healthcare personnel of fertility centers providing FP health care should undergo specific training and preparations to meet the transgender patient population specific demands and to overcome communication barriers, as previously reported by our group. By analyzing the time between referral and first cryopreservation, more accurate and evidence-based information may now be given to patients on how long they have to wait before starting GAHT. The fact that they only have to wait for approximately a month is information that might help promote the utilization of FP for individuals who want to begin GAHT as soon as possible. The aspect of equity is of relevance when reflecting over the application of the information gained in this study to the population of transgender women in the rest of Sweden. The healthcare provided for patients in the Stockholm region might differ to that available in other regions in Sweden.

5 | CONCLUSIONS

This study showed low sperm counts and hampered sperm motility in transgender women who underwent FP. There were significantly lower sperm counts and sperm concentration in semen samples of transgender women that had started GAHT prior to FP, compared to transgender women that had not started GAHT. Our study gives further support to the importance of thoroughly discussing parenthood plans and FP with transgender patients, preferably before starting GAHT. There has been an increase of transgender women presenting for FP in Stockholm, but the rate of FP remains low in this population. In this cohort, FP could be accessed by transgender women within 1 month from diagnosis. This information may be included in the FP counseling, and to support transgender women in making informed decisions regarding their future fertility options.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

KARW designed the study and provided economic and administrative support; JH and KARW collected the data; JH, ALVJ and FEL analyzed the data; KARW, JH, SA, ALVJ and FEL wrote the manuscript. All authors approved the last version of the manuscript.

ORCID

Kenny A. Rodríguez-Wallberg https://orcid.org/0000-0003-4378-6181
Frida E. Lundberg https://orcid.org/0000-0001-7061-7178

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