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3

Desire for children and fertility preservation in transgender and gender-diverse people: A systematic review

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A B S T R A C T

The decision to pursue one's desire for children is a basic human right. For transgender and gender-diverse (TGD) people, gender-affirming care may alter the possibilities to fulfill one's desire for children due to the impact of this treatment on their reproductive organs. We systematically included 76 studies of varying quality describing the desire for children and parenthood; fertility counseling and utilization; and fertility preservation options and outcomes in TGD people. The majority of TGD people expressed a desire for children. Fertility preservation utilization rates were low as there are many barriers to pursue fertility preservation. The most utilized fertility preservation strategies include oocyte vitrification and sperm banking through masturbation. Oocyte vitrification showed successful outcomes, even after testosterone cessation. Sperm analyses when banking sperm showed a lower quality compared to cis male samples even prior to gender-affirming hormone treatment and an uncertain recovery of spermatogenesis after discontinuing treatment.

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Introduction

The decision to pursue one's desire for children is a basic human right. Historically, a multitude of assumptions, misjudgments, and legislations have led to underexposure of the importance of child wish and parenthood in transgender and gender-diverse (TGD) people. In most countries, laws required sterilization to obtain legal gender affirmation. Therefore, TGD people were obligated to choose between the right to make a decision about their legal identity and the right to have children. Even though the United Nations called to outlaw forced sterilization in 2013, there are still several countries holding on to these basic human rights violating laws. The foremost concern against the reproduction of TGD people was the psychological effect of TGD parents on the child. Although available data do not support these concerns and actually show good quality relationships between TGD parents and their children and good psychological adjustments, TGD parents still experience a lot of stigmatization and discrimination [1–4].

TGD people may seek gender-affirming medical care at any age. For TGD adolescents who present in early puberty (Tanner $\geq$2), their medical transition may consist of reversible puberty suppression (PS) with gonadotropin-releasing hormone (GnRH) agonists to alleviate distress caused by the (further) development of secondary sex characteristics induced by puberty [5]. TGD adolescents who receive PS show a lower odds of lifetime suicidal ideation than TGD adolescents who wanted PS but did not receive this [6]. In addition, PS prolongs time for gender clarification and to mentally mature without the distress of permanent secondary sex characteristic development. When TGD adolescents desire to continue their gender-affirming treatment, gender-affirming hormone treatment (GAHT) is introduced to develop the secondary sex characteristics that align with the preferred gender identity. As GAHT is partly irreversible, it is important that TGD adolescents have the mental capacity to give informed consent before starting GAHT. In some countries, GAHT is introduced when sufficient mental capacity to give informed consent is reached, usually around 15 years of age onward. In some countries, the age of legal adulthood is used to determine when to start GAHT.

Although GAHT alleviates symptoms of gender dysphoria, increases general well-being, and decreases rates of depression and suicidality [7,8], there are significant consequences for fertility that should be considered prior to medical transition. Furthermore, if gender-affirming surgery (GAS) is desired in adulthood, infertility is irreversible in the case of gonadectomy.

Effects of hormone treatment on fertility in transgender and gender-diverse people assigned male at birth

GAHT for assigned male at birth (AMAB) people consists of estrogen supplementation to achieve feminization. This is usually combined with androgen deprivation therapy until gonadectomy to achieve demasculinization. Examples of androgen deprivation therapy include spironolactone, mostly prescribed in the US, GnRH agonists, mostly prescribed in Europe, and previously cyproterone acetate, which is no longer recommended by the European medicines agency due to an increased risk for developing intracranial meningiomas [9].

In AMAB people, spermatogenesis is supported by testosterone from Tanner stage 3 onward. When serum testosterone levels are within cisgender female reference ranges, this leads to strong suppression of spermatogenesis [10]. However, complete spermatogenesis or tubules containing spermatozoa may still be present in tissues at GAS [11–14].

AS PS may be initiated from Tanner stage 2, spermatogenesis may not be present at the time TGD AMAB adolescents start their medical transition. When continuing GnRH agonists as androgen deprivation therapy as part of their GAHT later in life, these adolescents may never develop spermatogenesis. A recent study showed TGD AMAB adults who initiated medical treatment with PS in Tanner stage 2 or 3 only had immature germ cells present in their orchiectomy specimens after GAS [14].

Theoretically, serum testosterone concentrations will increase after the cessation of PS or GAHT and provide adequate circumstances for the restoration of spermatogenesis. However, it is unknown when this may occur. In a study of cisgender male adolescents treated for precocious puberty, spermarche was reported 0.7–3 years after termination of GnRH agonist therapy [15]. For TGD AMAB people, this remains unclear.

Effects of hormone treatment on fertility in transgender and gender-diverse people assigned female at birth

GAHT for assigned female at birth (AFAB) people consists of testosterone to achieve masculinization. Oocyte maturation is dependent on the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Testosterone induces hypothalamic–pituitary–gonadal suppression, but LH and FSH are not completely inhibited [16,17]. Consequently, oocyte maturations are not always suppressed during testosterone treatment. Several studies showed that ovulations and pregnancies do occur among TGD people during testosterone treatment [16,18–20].

In TGD AFAB adolescents treated with PS, FSH and LH are reversibly inhibited. In cisgender AFAB adolescents treated with GnRH agonists for precocious puberty, LH and FSH arose back to normal after discontinuation [21], and long-term follow-up studies report a normal ovarian function [22], pregnancy rate, and outcome [23].

Currently, there are no long-term follow-up studies studying the effect of PS and testosterone on gonadal function and gametes. Histological studies at the time of GAS show normal histopathology similar to cisgender women [19,24], normal number, and distribution of the follicles. However, some changes in the cortical and stromal tissue [25,26] and polycystic ovarian morphology were described [27].

Access to reproductive health care

Several guidelines, including the World Professional Association for Transgender Health (WPATH), recommend to counsel all TGD people before starting any medical treatment on the impact on fertility and the fertility preservation (FP) options [28]. This is important as the desire for children may develop over time, while starting GAHT is a current priority for many TGD adolescents and young adults.

TGD people with the desire for children will sometimes require assisted reproductive technology (ART) using their fresh or banked gametes, including intrauterine insemination (IUI) or in vitro fertilization (IVF). Their reproductive plans may include the use of donor oocytes or sperm, or a gestational carrier. The European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) stated that medically assisted reproduction for TGD people cannot be denied from a human rights perspective, and they do not support concerns that children are harmed from being raised by TGD parents [29,30]. Even though access to reproductive health care seems to be improving for TGD people, there are still a lot of barriers for TGD people to overcome.

The objective of this systematic review is threefold. Firstly, to describe the desire for children and parenthood in TGD people. Secondly, to describe fertility counseling and utilization. Thirdly, to describe different fertility preservation options and outcomes in TGD people.

Methods

Literature review

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (www.prisma-statement.org) [31].

Search strategy

To identify the relevant publications, we conducted systematic searches in the bibliographic databases PubMed, Embase.com, and APA PsycINFO from 2012 up to July 15, 2022, in collaboration with a medical information specialist. The year 2012 was chosen because the seventh edition of the WPATH standards of care emphasized the importance of discussing fertility. The following terms were used (including synonyms and closely related words) as index terms or free-text words:

"Fertility," "Fertility preservation," "Child wish," "Transgender persons."

The references of the identified articles were searched for relevant publications. All languages were accepted. Duplicate articles were excluded by a medical information specialist using Endnote X20.0.1 (Clarivatetm), following the Amsterdam Efficient Deduplication (AED) method [32] and the Bramer method[33].

The full search strategies for all databases can be found in Appendix A.

Selection process

Studies were included for data assessment if they met one of the following inclusion criteria: (i) desire for children in TGD people; (ii) TGD parenthood; (iii) fertility preservation counseling and utilization; and (iii) fertility preservation methods for TGD people. Determined exclusion criteria were (i) reviews; (ii) qualitative data; (iii) abstracts; and (iv) certain publication types: editorials, letters, legal cases, interviews, etc.

Two reviewers [Stolk (TS) and Asseler (JA)] independently screened all potentially relevant titles and abstracts as well as full texts for eligibility. Conflicts were resolved through discussion and, if necessary, by consulting a third person [van Mello (NM)].

Data assessment

Two reviewers (TS and JA) independently appraised the methodological quality of the included studies using the Joanna Briggs Institute (JBI) critical appraisal tools [34] for cohort studies, analytical cross-sectional studies, and case series. Case reports were not appraised.

Results

Search results

The literature search generated a total of 2641 references: 937 in PubMed, 967 in Embase. com, and 737 in APA PsycINFO. After removing duplicates of references that were selected from more than one database, 1801 references remained. A flow chart of the search and selection process is presented in Fig. 1.

Sample description

We included 76 papers in total. The 76 studies came from 16 different countries; 35 from the US, 7 Belgium, 7 Israel, 4 the UK, 3 Australia, 3 the Netherlands, 2 Canada, 2 Sweden, 1 Brazil, 1 France, 1 Germany, 1 Japan, 1 Mexico, 1 New Zealand, 1 Thailand, and 1 Turkey.

Because of the large number of papers included in this systematic review, we chose to display the results in three parts in line with our objectives: (1) desire for children and parenthood, (2) fertility counseling and utilization, and (3) fertility preservation options and outcomes.

For our first objective, 19 studies were included that described a desire for children and parenthood, 14 about TGD adults, and 6 about TGD adolescents (Tables 1 and 2). Of these 19 studies, 78% were cross-sectional studies. We included another 5 papers about pregnancy (Table 6). For our second objective, 22 studies were included that described fertility counseling and utilization, 13 about TGD adults, and 9 about TGD adolescents. Of these studies, 45% were cross-sectional and 41% retrospective chart reviews (Tables 3 and 4). For our third objective, 36 studies were included that described fertility preservation options. A total of 17 papers discussed oocyte cryopreservation; 59% case reports and 41% retrospective studies (Table 5). Three papers discussed ovarian tissue cryopreservation, of which 2 were observational-prospective studies and 1 was a cross-sectional study (Table 7). Thirteen papers discussed semen cryopreservation, 61% retrospective (Table 8). Three papers reported on testicular tissue

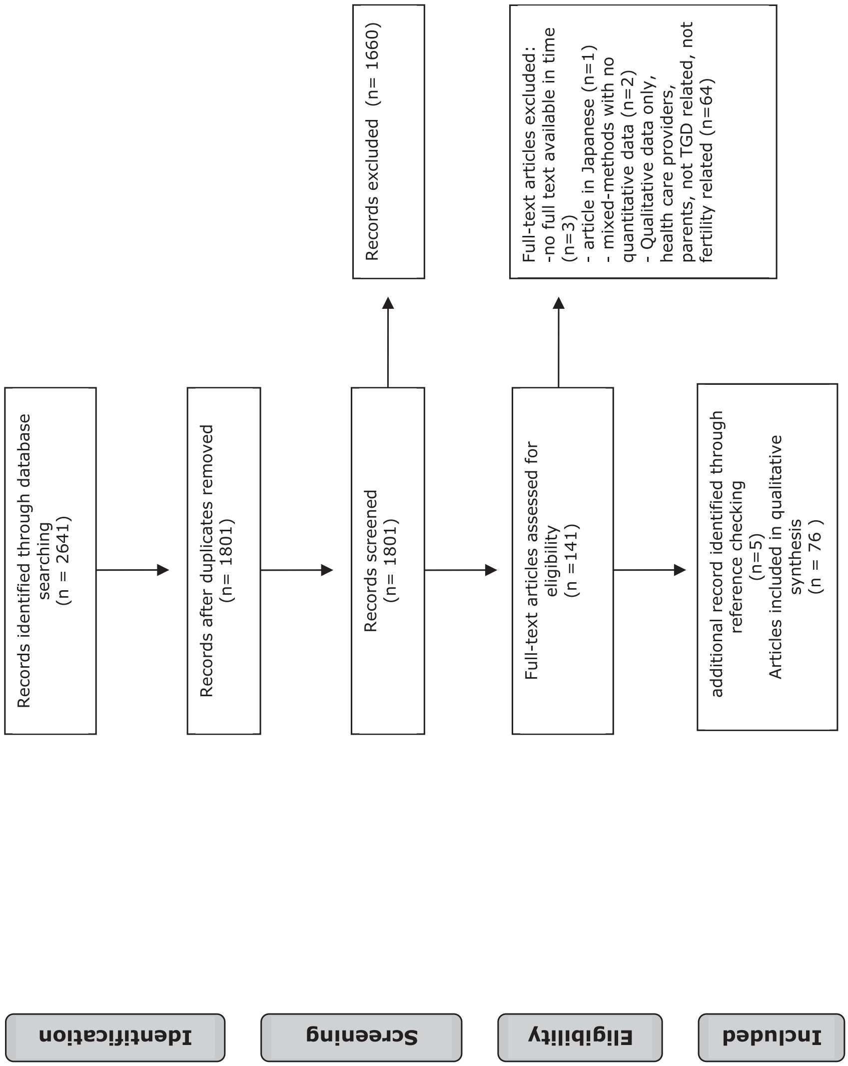

Fig. 1. Flowchart of the search and selection procedure of studies.

Table 1
Desire for children in TGD adolescents.

Author (year) country	Study design	Study period (years)	Sample size, population	Mean age ± SD/median age (range) (years)	Objectives	Outcomes
Chen et al. (2018) USA [35]	Online survey	2016	N = 156 TGD adolescents (16.7% AMAB, 83.3% AFAB) interested in cisgender males 9 participant received GAHT	16.1 ± 0.97	To study reproductive desires of TGD adolescents who may seek GAHT	Desire for children 48.7% interested in adoption: 70.5%
Chiniara et al. (2019) Canada [36]	Cross-sectional	2016–2017	N = 79 adolescents N = 64 AFAB 52% had PS and 35% GAHT N = 15 AMAB 87% had PS and 53% GAHT	AFAB 70% between 16 and 18 AMAB 60% between 16 and 18	To investigate the views of TGD adolescents concerning fertility preservation and reproductive and life priorities.	Desire for children: 66% AFAB, 67% AMAB Biological relatedness: 9% AFAB and 7% AFAB Interested in adoption: 72% AFAB, 80% AMAB
Komorowski et al. (2021) USA [38]	Retrospective chart study	2012–2017	N = 67 TGD adolescents (22 AMAB and 45 AFAB)	15	Characterize the epidemiology and differences in fertility counselling, referral, and utilization of FP between AMAB and AFAB TGD adolescents.	Desire for children: 56% Biological relatedness: 24%
Strang et al. (2018) USA [37]	Prospective pilot trial	NA	N = 25 TGD adolescents	16 (12–19)	To assess TGD youth attitudes regarding (1) the potential impact of gender-affirming hormone therapy on fertility and (2) fertility preservation options.	Desire for children: 54% Biological relatedness: 9.1%
Persky et al. (2020) USA [41]	Cross-sectional survey study	2017	N = 66 TGD adolescents 59% had received GAHT	16.8 ± 2.1	To understand TGD adolescents toward FP decision-making.	Biological relatedness: 20%
Morrison et al. (2020) USA [42]	Cross-sectional survey study	2016–2017	N = 23 TGD adolescents and young adult (17AFAB, 5AMAB) 18/23 received PS or GAHT	16.2 ± 2.5	Characterize the knowledge about fertility and attitudes about future parenthood in a sample of TGD youth.	Interested in adoption: 70%
Langer et al. (2020) USA [39]	Cross-sectional, survey study	2019–2020	N = 21 TGD adolescents AFAB N = 217 cisgender adolescents AFAB	16.06 ± 1.87 Between 13 and 19	To describe fertility desires in healthy adolescent females and to explore associations of fertility desire with conditions and therapies potentially compromising fertility.	Desire for children TGD vs. cisgender: (67% vs. 93%, P < 0.001)

SD: standard deviation.
NA: not applicable.
TGD: transgender and gender-diverse.
AFAB: assigned female at birth.
AMAB: assigned male at birth.
GAHT: gender-affirming hormone therapy.
FP: fertility preservation.

Table 2
Desire for children in TGD adults.

Author (year) country	Study design	Study period (years)	Sample size, population	Mean age ± SD/median age (range) (years)	Objectives	Outcomes
Alpern et al. (2022) Israel [43]	Prospective cohort study	2017–2019	N = 188 TGD adults N = 79 TGD AMAB N = 81 TGA AFAB	27.8 ± 7.78 26.68 ± 7.46	To assess the fertility aspirations and fertility preservation rates among TGD people of reproductive age, and to identify factors affecting their decisions of whether or not to preserve fertility.	Desire for children: children 61.7% AFAB and 67.4% AMAB
Auer et al. (2018) Germany [47]	Cross-sectional multicenter questionnaire study	2013–2016	N = 99 TGD AMAB N = 90 TGD AFAB. Of these, 26 of each sex were just about to start medical treatment	No GAHT: TGD AMAB:41 (26.25–47.75) TGD AFAB: 25 (20–32.5) With GAHT: TGD AMAB:41 (31–51) TGD AFAB: 33 (24.75–37)	To study how the desire for children and the use of fertility preservation options varies among TGD people AMAB and AFAB in different transitioning stages in Germany	Desire for children: AMAB: 65.4% prior GAHT vs. 69.9% during GAHT AFAB: 53% prior GAHT vs. 46.9% during GAHT Parents: 31.5% AFAB and 10.9% AMAB
Defreyne et al. (2020) Belgium [48]	Online survey	2017	N = 254 AMAB TGD people	43.0 (31.0–53.0)	To study parental desire in a nonclinical sample AMAB TGD people.	Desire for children: 22.5% TGD parents: 32.9%
Defreyne et al. (2020) Belgium [49]	Online survey	2017	N = 172 AFAB TGD people	24.0 (20.0–29.0)	To study parental desire in a nonclinical sample AFAB TGD people.	Desire for children: 39.0% TGD parents: 9.3%
Durcan et al. (2022) Turkey [52]	Cross-sectional comparative study	2021	N = 171 TGD adults (110 AFAB and 61 AMAB) N = 243 matched cisgender volunteers (142 AMAB 101 AFAB)	TGD: 26 (23–32) Cisgender: 26 (24–30)	Quantitatively display fertility desire from the perspective of TGD individuals.	Same fertility desire in TGD people compared to cisgender people.
Mattawanon et al. (2021) Thailand [53]	Cross-sectional study	2019	N = 303 TGD adults AMAB	25 (IQR 21–29)	To explore the desires and barriers to fertility preservation among TGD AMAB in Thailand.	Desire for children: 30.4%
Mattelin et al. (2022) Sweden [55]	Retrospective cohort study	2013–2018	N = 78 TGD AMAB N = 164 TGD AFAB	24.4 ± 6.6 23.9 ± 5.8	Which factors influence the decision to cryopreserve oocytes and sperm.	Desire for children: 69.5% AFAB and 82.1% AMAB
		2019–2020		27.6 ± 8.2		Desire for children: 59.9%

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Table 2 (*continued*)

Author (year) country	Study design	Study period (years)	Sample size, population	Mean age ± SD/median age (range) (years)	Objectives	Outcomes
Morong et al. (2022) USA [45]	Multicenter cross-sectional study		N = 80 TGD adults (13 AMAB and 64 AFAB)		Assess parenting intentions, knowledge and attitudes regarding fertility preservation, and barriers to achieving parenthood in TGD adults.	
Riggs et al. (2016) Australia [51]	Online survey	2014	N = 160 TGD adults	With children: 45.15 ± 11.04 Without children: 33.07 ± 11.21	To explore parenting in TGD people.	Desire for children: 18.4% Parents: 24.4%
Riggs et al. (2018) Australia [50]	Mixed method	2018	N = 409 TGD adults	28.54 ± 11.25	To explore genetic relatedness, GAHT, fertility preservation utilization relation to fertility in TGD people, and what influences decision-making.	Desire for children: without children: 18.8% with children: 33.6% Parents: 18.6%
Wierckx et al. (2012) Belgium [46]	Cross-sectional questionnaire study	1987 and 2009	N = 50 TGD AFAB	37 ± 8.2 (22–54)	To provide data on reproductive wishes of TGD AFAB people after GAS.	Desire for children: 54% Parents: 22%
Salinas-Quiroz et al. (2019) Mexico [54]	Online survey	2015	N = 88 TGD people	NA	Examine parenting aspiration among a sample of LGBTQ community in Mexican.	Desire for children: 36%
Silva et al. (2022) Brazil [57]	Web-based cross-sectional survey study	2014–2015	N = 670	NA	To describe general characteristics of TGD parents, highlight aspects of their relationship with their children, and explore experiences with discrimination, compared with transgender nonparents.	Parents: 6.6%

NA: not applicable.
TGD: transgender and gender-diverse.
AFAB: assigned female at birth.
AMAB: assigned male at birth.
GAS: gender-affirming surgery.

Table 3
Fertility preservation counseling and utilization TGD adolescents.

Author (year) country	Study design	Study period (years)	Sample size, population	Mean age ± SD/median age (range) (years)	Objectives	Outcomes
Chen et al. (2017) USA [58]	Retrospective chart review	2013–2016	N = 105 TGD adolescents (28AMAB, 77 AFAB)	16.5 (14.2–20.6)	Describe fertility preservation utilization by TGD adolescents	All had fertility counseling
Chiniara et al. (2019) Canada [36]	Cross-sectional questionnaire study	2016–2017	N = 79 adolescents N = 64 AFAB 52% had PS and 35% GAHT N = 15 AMAB 87% had PS and 53% GAHT	AFAB 70% between 16 and 18 AMAB 60% between 16 and 18	To investigate the views of TGD adolescents concerning fertility preservation and reproductive and life priorities.	All had fertility counseling 0% fertility preservation utilization
Segev-Becker et al. (2020) Israel [59]	Retrospective chart review	2013–2018	N = 106 TGD adolescents (47 AMAB, 59 AFAB)	15.5 (4.6–18.5)	To describe patient characteristics at presentation, management, and fertility preservation rates among TGD adolescents.	Fertility counseling: 90% Fertility preservation utilization: 16% (14 AMAB, 3 AFAB)
Nahata et al. (2017) USA [60]	Retrospective chart review	2014–2016	N = 73 TGD adolescents (50 AFAB, 23 AMAB)	AFAB: 15.0 (9–18) AMAB: 16.0 (14–18)	To examine the rates of fertility counseling and utilization of fertility preservation among TGD adolescents.	Fertility counseling: 98.6% Fertility preservation utilization: 9%
Nahata et al. (2020) USA [40]	Cross-sectional questionnaire study	NA	N = 44 TGD adolescents 81% AFAB	16.30 ± 1.84	To examine attitudes toward fertility/parenthood; and self-reported counseling experiences and fertility preservation in TGD adolescents.	Fertility preservation utilization: 2.7% (2 AMAB)
Cooper et al. (2022) USA [62]	Retrospective review study	2015–2019	N = 132 TGD adolescents before PS/GAHT	15.7 AMAB 15.5 AFAB	Assess fertility preservation utilization interest among TGD adolescents and young adults.	Fertility counseling: 88% Fertility preservation utilization: 6.8% (6 AMAB, 2 AFAB)
Brik et al. (2019) The Netherlands [61]	Observational study	2011–2017	N = 35 TGD AMAB adolescents	14.8 ± 1.9	To examine the rate of attempted fertility preservation TGD AMAB adolescents who started GnRH agonist treatment.	91% fertility counseling
McCallion et al. (2021) UK [65]	Retrospective chart review	2011–2019	N = 91 TGD adolescents (65% AFAB, 35% AMAB) before start of PS	14.6 (8.8–17.6)	Explore the uptake of the fertility preservation service.	Fertility preservation utilization: 6,25% (5 AMAB, 1 AFAB)
	Retrospective chart study	2012–2017	N = 67 TGD adolescents (22 AMAB and 45 AFAB)	15	Characterize the epidemiology and differences in fertility	

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Table 3 (*continued*)

Author (year) country	Study design	Study period (years)	Sample size, population	Mean age ± SD/median age (range) (years)	Objectives	Outcomes
Komorowski et al. (2021) USA [38]					counselling, referral, and utilization of fertility preservation between AMAB and AFAB TGD adolescents.	Fertility preservation utilization: 3.0% (2AMAB)
Pang et al. (2020) Australia [64]	Retrospective chart review	2003–2017	N = 102 TGD adolescents (49 AFAB and 53 AMAB)	15.6 (10.8–18.3)	To examine fertility preservation use among TGD adolescents.	All received FP counseling 0 AFAB pursued FP 62% AMAB pursued FP (22 via masturbation and 11 via TESE)
Wakefield et al. (2019) USA [63]	Retrospective chart review	2010–2017	N = 66 TGD adolescents and young adults (28 AMAB and 38 AFAB)	16.8 ± 3.2 (7–25)	To examine fertility discussion and referral in nonmetropolitan youth.	Fertility counseling: 78.8% Referral: 11 Utilization: 2 AMAB

SD: standard deviation.
NA: not applicable.
TGD: transgender and gender-diverse.
AFAB: assigned female at birth.
AMAB: assigned male at birth.
GAHT: gender-affirming hormone therapy.
FP: fertility preservation.

Table 4
Fertility preservation counseling and utilization in TGD adults.

Author (year) country	Study design	Study period (years)	Sample size, population	Mean age ± SD/median age (range) (years)	Objectives	Outcomes
Morong et al. (2022) USA [45]	Cross-sectional Multicenter study	2019–2020	N = 80 TGD adults (13 AMAB and 64 AFAB)	27.6 ± 8.2	Assess parenting intentions, knowledge and attitudes regarding fertility preservation, and barriers to achieving parenthood in TGD adults.	Fertility counseling 50%
Ker et al. (2021) New Zealand [69]	Online survey	2018	N = 1178 TGD people N = 419 received GAHT or GAS	29.5	Examine fertility preservation information and services in Aotearoa New Zealand.	Fertility counseling 33.7% Fertility preservation utilization: 15.8%
Defreyne et al. (2020) Belgium [48]	Online survey	2017	N = 254 AMAB TGD people	43.0 (31.0–53.0)	To study parental desire in a nonclinical sample AMAB TGD people.	Fertility counseling 50.6% Fertility preservation utilization: 8.7%
Defreyne et al. (2020) Belgium [49]	Online survey	2017	N = 172 AFAB TGD people	24.0 (20.0–29.0)	To study parental desire in a nonclinical sample AFAB TGD people.	Fertility counseling 36.5% Fertility preservation utilization: 9%
Riggs et al. (2018) Australia [50]	Mixed method	2018	N = 409 TGD adults	28.54 ± 11.25	To explore genetic relatedness, GAHT, fertility preservation utilization relation to fertility in TGD people, and what influences decision-making.	Fertility preservation utilization: 15.8% Fertility preservation utilization: 7%
Vyas et al. (2021) USA [56]	Cross-sectional follow-up survey	2019	N = 70 TGD adults (34% AFAB, 66% AMAB)	38.5 ± 16.8 at follow-up	To query TGD people their desire for fertility preservation, perceived barriers to access care, and decisional regret.	Fertility preservation utilization: 6% Parents: 30%
Mattawanon et al. (2021) Thailand [53]	Cross-sectional study	2019	N = 303 TGD adults AMAB	25 inter quartile range (21–29)	To explore the desires and barriers to fertility preservation among TGD AMAB in Thailand.	Fertility preservation utilization: 5.3%
Rogers et al. (2021) UK [70]	Retrospective study	2015–2020	N = 3667 TGD adults (67.2% AMAB, 28.7% AFAB)	(10 – 85)	To formally categorize the reasons that TGD people do and not store gametes prior to hormonal treatments.	Fertility preservation utilization: 4.4%
Auer et al. (2018) Germany [47]	Cross-sectional multicenter questionnaire study	2013–2016	N = 99 TGD AMAB N = 90 TGD AFAB. Of these, 26 of each group were just about to start medical treatment.	No GAHT: TGD AMAB:41 (26.25–47.75) TGD AFAB: 25 (20–32.5) With GAHT: TGD AMAB:41 (31–51)	To study how the desire for children and the use of fertility preservation options varies among TGD people AMAB and AFAB in different transitioning stages in Germany.	Fertility preservation utilization: 2.6% (3 AMAB and 2 AFAB

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Table 4 (*continued*)

Author (year) country	Study design	Study period (years)	Sample size, population	Mean age ± SD/median age (range) (years)	Objectives	Outcomes
				TGD AFAB: 33 (24.75 −37)		
Mattelin et al. (2022) Sweden [55]	Retrospective cohort study	2013–2018	N = 78 TGD AMAB N = 164 TGD AFAB	24.4 ± 6.6 23.9 ± 5.8	Which factors influence the decision to cryopreserve oocytes and sperm.	Fertility preservation utilization: 34.4% AFAB and 76% AMAB
Eustache et al. (2021) French [68]	Retrospective and survey study	2019–2020	N = 581 TGD people (378 AMAB, 203 AFAB) referred to a FP center	22.39 ± 6.54 AMAB 23.89 ± 7.00 AFAB 19.6 ± 4.35	To evaluate the distribution of care on the French territory concerning fertility preservation and sperm donation in transgender individuals.	Fertility preservation utilization: 65.6% AMAB and 11.3% AFAB
Alpern et al. (2022) Israel [43]	Prospective cohort study	2017–2019	N = 188 TGD adults (n = 97 AMAB, n = 91AFAB) Group 1: >18 ≤ 25 Group 2: >25 < 41	AMAB: 27.8 ± 7.78 (19 −57) AFAB: 26.68 ± 7.46 (18 −50)	Fertility preservation rates and decision-making factors of TGD adults.	Fertility preservation utilization: 40.4% AMAB versus 5.8% AFAB
Amir et al. (2020) Israel [67]	Retrospective cohort study	2017–2019	N = 112 TGD adults and adolescents N = 56 TGD AMAB N = 56 TGA AFAB	22.68 ± 5.387 20.98 ± 6.735	To examine the fertility preservation rates among TGD adolescents and adult study participants who received comprehensive counselling from fertility specialists, and to compare the fertility preservation rates between TGD AMAB and AFAB.	Fertility preservation utilization: 85.7% AMAB versus 35.7% AFAB

SD: standard deviation.
NA: not applicable.
TGD: transgender and gender-diverse.
AFAB: assigned female at birth.
AMAB: assigned male at birth.
GAHT: gender-affirming hormone therapy.
FP: fertility preservation.

Table 5
Oocyte and embryo cryopreservation in transgender and gender-diverse people assigned female at birth.

Authors, (year), country	Fertility preservation method	Study design	Study period (years)	Sample size, population	Mean age ± SD/median age (range) (years)	GAHT mean length ±SD/median length (range) (months)	Objectives	Outcomes
Adeleye et al. (2019) USA [71]	Oocyte cryopreservation	Retrospective chart review	2015–2019	N = 13 TGD AFAB with N = 6 no prior testosterone use N = 7 prior testosterone use N = 13 matched cisgender women	All TGD adults 22.4 (19.4–32.5) No testosterone 20.3 (15.2–25.5) With testosterone 26.9 (20.9–36.5)	Testosterone exposure 46 months discontinuation 6 (1–13)	To compare ovarian stimulation and pregnancy outcomes between TGD people with and without a history of testosterone use and to cisgender women.	TGD AFAB without testosterone use had a median of 25.5 [IQR 18–28] oocytes collected compared to 12 [IQR 4–26] oocytes among TGD AFAB with a history of testosterone use p = 0.038. Testosterone exposure did not have a significant impact on markers of follicular function or oocyte maturity. Two ongoing pregnancies with cisgender partner and one abortion.
Amir et al. (2020) Israel [75]	Oocyte cryopreservation	Retrospective cohort study	2017–2019 2013–2019	N = 9 TGD AFAB and N = 39 cisgender female adolescent	16.4 ± 1.1 vs. 15.5 ± 1.3, respectively	No medication prior to FP	Ovarian stimulation outcomes among TGD AFAB adolescents compared with fertile cisgender women.	There were no significant differences in the number of retrieved oocytes between the two groups (30.6 ± 12.8 vs. 22 ± 13.2), number of MII oocytes (25.6 ± 12.9 vs. 18.8 ± 11.2), or maturity rates (81.5 ± 10.0% vs. 85.4 ± 14.6%).
Amir et al. (2020) Israel [72]	Oocyte cryopreservation	Retrospective cohort study	2017–2019	N = 12 TGD AFAB N = 6 no prior testosterone use N = 6 testosterone use	No testosterone 23.3 ± 4 Testosterone 30.3 ± 3.8 Cisgender women 29.1 ± 3.1	Testosterone exposure was 77 ± 55.3 (14–144) discontinuation of testosterone 9.3 ± 5.9 (5–21)	To compare ovarian stimulation outcomes between TGD people with and without a history of testosterone	No differences in the number of oocytes retrieved, in the number of MII oocytes, and in the oocyte maturity rates.

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Table 5 (*continued*)

Authors, (year), country	Fertility preservation method	Study design	Study period (years)	Sample size, population	Mean age ± SD/median age (range) (years)	GAHT mean length ±SD/median length (range) (months)	Objectives	Outcomes
				N = 12 matched cisgender women			use and to cisgender women.	
Barrett et al. (2022) USA [84]	Oocyte cryopreservation	Retrospective Case series	2009–2021	n = 20 TGD AFAB adolescents and young adults n = 2 prior testosterone use	16 (12–25)	Length of testosterone exposure NA discontinued for 2–3 months.	To review our experience with oocyte cryopreservation in TGD adolescent and young adult and oocyte cryopreservation outcomes.	95% (19/20) underwent successful transvaginal oocyte aspiration, with a median of 22 oocytes retrieved, and all retrievals resulted in frozen MII oocytes (median 15, range 3–35).
Broughton et al. (2017) [76]	Oocyte cryopreservation	Case series	2015–2016	2 couples of TGD AFAB adults with cisgender wife	30	First patient testosterone use 26 and discontinued 3. Second patient no prior GAHT	Family building in the TGD population.	One blastocyst created from each couple was thawed and transferred into the cisgender partner's uterus. Resulting in a successful intrauterine pregnancy.
Chen et al. (2018) USA [85]	Oocyte cryopreservation	Retrospective case series	NA	N = 5 AFAB adolescents	Between 14 and 18	No GAHT	Report the feasibility of ovarian stimulation and oocyte cryopreservation prior to their initiating testosterone treatment.	The mean number of oocytes retrieved was 18.2 (range 11–28), of which a mean of 14.2 oocytes (range 8–25) were mature and cryopreserved.
Cho et al. (2020) Canada [78]	Oocyte cryopreservation	Case report	NA	TGD AFAB adult	28	3 years testosterone exposure, no discontinuation	To study the feasibility of fertility preservation in a transgender man without an extended period of androgen cessation.	13 oocytes were retrieved; 11 were mature and vitrified. The total time off testosterone was 24 days. He stopped one week before GnRH agonist administration.
Greenwald et al. (2022) USA [82]	Oocyte cryopreservation	Case report	2017	TGD AFAB adult	33	10 year testosterone exposure and no discontinuation	To study the feasibility of fertility preservation in a TGD AFAB without an extended period of androgen cessation.	Successful oocyte retrieval and live birth.

Gale et al. (2021) Canada [79]	Oocyte cryopreservation	Case report	NA	TGD AFAB adult	20	18 months testosterone exposure, no discontinuation	Ovarian stimulation for the purposes of oocyte cryopreservation in a TGD AFAB without cessation of long-term testosterone therapy.	Cryopreservation of 22 mature oocyte.
Insogna et al. (2020) USA [86]	Oocyte cryopreservation	Case report	NA	N = 4 TGD AFAB patients	Between 15 and 21	1 patient had 2-year testosterone exposure discontinued for 3 months 1 patient 66 days after placing PS implant.	Outlines the feasibility of oocyte cryopreservation for transgender male adolescents after varying degrees of exposure to pubertal blockers and/or testosterone.	All patients had cryopreserved mature oocytes (MII) range 6–18.
Israeli et al. (2022) Israel [73]	Oocyte cryopreservation	Retrospective study	2016–2021	N = 7 TGD AFAB adults N = 34 cisgender women	30.2 ± 3.5 35.1 ± 1.8, respectively	Testosterone use 99.7 ± 49.2 (14–156) All discontinued testosterone 6.5 ± 2.1 (4–10)	Effects of testosterone treatment on oocyte fertilization and preimplantation embryo development among TGD people.	The mean number of oocytes retrieved from the TGD adults (21 ± 10.9) was significantly higher compared with the mean number of oocytes retrieved from the cisgender women who had undergone fertility treatment (11.5 ± 5.7). Development and quality of embryos from testosterone-exposed TGD people were comparable to those of embryos from cisgender women.
Leung et al., 2019 USA [74]	Oocyte cryopreservation	Retrospective cohort study	2010–2018	N = 26 TGD AFAB adults N = 130 matched cisgender women	28.3 ± 6.7	Testosterone use 43.9 ± 31.0 Time off testosterone 4.5 ± 3.5	To investigate FP outcomes in a TGD AFAB cohort and compare the results with those of a matched cisgender cohort.	More oocytes were retrieved in the TGD cycles compared with cisgender cycles 17.7 ± 6.1 oocytes frozen 4.2 ± 0.6 embryos frozen. IVM with transfer to self (n = 2) or partner (n = 5). All 7

(*continued on next page*)

Table 5 (*continued*)

Authors, (year), country	Fertility preservation method	Study design	Study period (years)	Sample size, population	Mean age ± SD/median age (range) (years)	GAHT mean length ±SD/median length (range) (months)	Objectives	Outcomes
								patients had successful pregnancies.
Martin et al. (2021) USA [87]	Oocyte cryopreservation	Case report	NA	AFAB TGD adolescent	15	Started GnRH agonist at Tanner stage II	To report ovarian hyper stimulation and oocyte cryopreservation in a TGD AFAB adolescent after suppression with a GnRH agonist.	22 mature oocytes were retrieved.
Maxwell et al. (2017) USA [77]	Oocyte cryopreservation	Case report	NA	2 TGD AFAB adults	30 and 32	No precious GAHT	Show family-building options for TGD AFAB people.	Oocyte cryopreservation and successful pregnancy in intimate partner from cryopreserved oocyte with 2 healthy twin pregnancies and live births.
Resende et al. (2020) Brasil [80]	Oocyte cryopreservation	Case report	NA	TGD AFAB adult and cisgender women	34	2 years testosterone exposure	First case in Brazil involving a TGD adult and a cisgender woman attempting to form a family.	Successful preservation with 5 embryos and one ongoing pregnancy in cisgender partner.
Stark et al. (2022) USA [81]	Oocyte cryopreservation	Case report	2020–2021	Two TGD AFAB adult	27	Both continued testosterone throughout the FP process	To study the feasibility of fertility preservation in a TGD AFAB without an extended period of androgen cessation.	Successful oocyte cryopreservation of 22 and 9 mature oocytes.
Wallace et al. (2014) USA [83]	Oocyte cryopreservation	Case report	NA	TGD AFAB adolescent	17	No previous GAHT	First documented case report of oocyte cryopreservation in TGD adolescent.	Successful cryopreservation: 35 MII oocytes were cryopreserved.

SD: standard deviation.
NA: not applicable.
TGD: transgender and gender-diverse.
AFAB: assigned female at birth.
AMAB: assigned male at birth.
GAHT: gender-affirming hormone therapy.
FP: fertility preservation.
IVM: in vitro maturation.
MII: Meiosis II.
COC: cumulus-oocyte complexes.

Table 6
Pregnancy in transgender and gender-diverse adults assigned female at birth.

Authors, (year), country	Reproduction method	Study design	Study period (years)	Sample size, population	Mean age ± SD/ median age (range) (years)	GAHT Mean length ±SD/median length (range) (months)	Objectives	Outcomes
Light et al. (2014) USA [89]	Pregnancy	Cross-sectional survey study	2013	41 TGD AFAB	28 ± 6.8	N = 25 used testosterone before pregnancy 40% less than 1 year, 20% more than 10 years.	To help guide practice and further investigation in TGD AFAB who had been pregnant and delivered after transitioning.	37% were multiparous. 61% reported using testosterone before pregnancy. 80% resumed menstruation within 6 months after discontinuation. 20% conceived while still amenorrheic. 2/3 of the pregnancies were planned. 68% stopped testosterone to become pregnant. All conceived between 1 and 6 months. 20% ART and 8% fertility drug. Pregnancy, delivery, and birth outcomes did not differ according to prior testosterone use.
Hahn et al. (2019) USA [90]	Pregnancy	Case report	NA	TGD AFAB young adult	20	5 months	Clinical guidance for providing prepregnancy, prenatal, intrapartum, and postpartum care to TGD people who desire pregnancy.	Achieved pregnancy two months after discontinuing testosterone via intercourse. Uncomplicated labor and vaginal delivery after spontaneous onset of labor at 40 weeks of gestation. The healthy newborn had no signs of androgenizing effects from in utero testosterone exposure.
Hassan et al. (2022) USA [92]	Pregnancy	Case report	NA	TGD AFAB young adult	21	2 years	To study TGD AFAB pregnancy.	Menstrual period one month after discontinuing testosterone and pregnancy the following month. Pregnancy was

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Table 6 (*continued*)

Authors, (year), country	Reproduction method	Study design	Study period (years)	Sample size, population	Mean age ± SD/ median age (range) (years)	GAHT Mean length ±SD/median length (range) (months)	Objectives	Outcomes
								achieved via vaginal intercourse with cismale partner. No significant complications and successfully delivery via *C*-section.
Leonard et al. (2022) USA [20]	Pregnancy	Population-based cohort study	2016 −2019	N = 498 fathers giving birth	30.8 (6.8)	NA	To evaluate obstetrical and birth outcomes comparing birthing fathers to birthing mothers who are not likely to be sexual and/or gender minority.	33% were nulliparous. Fathers giving birth in any partnership did not experience significant differences in obstetrical and birth outcomes from mothers with male partners.
Moseson et al. (2020) USA [88]	Pregnancy	cross-sectional online survey study	NA	N = 1694 TGD people AFAB	NA	28% ever used testosterone	To collect data on pregnancy intentions and outcomes among TGE people assigned female or intersex at birth in the United States.	12% reported ever being pregnant of the 12%, 55% nulliparous. The most common outcome was live birth (n = 169, 39%), followed by miscarriage (n = 142, 33%) and abortion (n = 92, 21%). 54% were not trying to get pregnant. 12 respondents reported 15 pregnancies that occurred after initiating testosterone. Three respondents reported four pregnancies while using testosterone. Two of these four pregnancies ended in miscarriage (one after five months of testosterone use, one after six months of testosterone use); one ended in abortion (after four months of testosterone use); and the outcome

Table 6 (*continued*)

Authors, (year), country	Reproduction method	Study design	Study period (years)	Sample size, population	Mean age ± SD/ median age (range) (years)	GAHT Mean length ±SD/median length (range) (months)	Objectives	Outcomes
								and testosterone duration for the fourth pregnancy were not reported. Eight of the 12 respondents reported stopping testosterone one month prior to getting pregnant. Across all 1694 TGE respondents, 11% (n = 186) desired future pregnancy, and an additional 16% (n = 275) were uncertain.
Yoshida et al. (2022) Japan [91]	Pregnancy	Case report	NA	TGD AFAB	25	3 years	Case of a TGD AFAB person who, while undergoing hormone therapy, became pregnant.	No planned pregnancy, at 23 weeks it was too late for an abortion. He discontinuation testosterone at 23 weeks. Spontaneous vaginal delivery at 38 weeks gestation. At 3 years after birth, no developmental abnormalities have been observed in the child.

SD: standard deviation.
NA: not applicable.
TGD: transgender and gender-diverse.
AFAB: assigned female at birth.
GAHT: gender-affirming hormone therapy.

cryopreservation and testicular sperm extraction: 1 prospective, 1 retrospective, and 1 case report (Table 9).

The quality assessment using the JBI checklist is shown in Supplementary Appendix B.

Part 1: desire for children and parenthood

Desire for children in transgender and gender-diverse adolescents

Seven studies reported on the desire for children in TGD adolescents and two of these included data on barriers regarding parental desire (see Table 1). The majority of the TGD adolescents' participants reported to have a future desire for children (48.7%–67%) [35–39]. However, many wondered, or did not know, if their feelings about having a child may change in the future [37,40]. Some participants feel

Table 7
Ovarian tissue cryopreservation and in vitro maturation in transgender and gender-diverse people assigned female at birth.

Authors, (year), country	Fertility preservation method	Study design	Study period (years)	Sample size, population	Mean age ± SD/median age (range) (years)	GAHT Mean length ±SD	Objectives	Outcomes
De Roo et al. (2017) Belgium [24]	Ovarian tissue cryopreservation	Observational, prospective cohort study	2013–2015	N = 40 TGD AFAB young adults	24.30 ± 6.15	58.18 ± 26.57 weeks of testosterone	Study the effect of prolonged androgen therapy on ovarian histology and fertility preservation perspectives.	COCs were retrieved of the medulla after gonadectomy. After 48 h IVM, 34.3% MII oocytes were observed (n = 27 patients) with 87.1% having a normal spindle pattern structure. This confirms the IVM potential of COC.
Lierman et al. (2017) Belgium [93]	Ovarian tissue cryopreservation	Observational, prospective cohort study	NA	N = 16 TGD AFAB adults	24.1 ± 6.1	53.6 ± 21.0 weeks	Study ovarian tissue cryopreserved as fertility preservation option at the moment of surgery.	After 48 h IVM, 38.1% of COCs were at MII stage. 85.7% showed normal spindle structure and 92.2% chromosomes alignment after warming.
Lierman et al. (2021) Belgium [94]	Ovarian tissue cryopreservation	Cross-sectional study	2015–2019	N = 83 TGD AFAB adults	20	Median 24 month testosterone	Study ovarian tissue cryopreserved as fertility preservation option at the moment of surgery.	1903 COCs were harvested. 23.8% oocytes reached the MII stage after IVM, after vitrification and

warming ICSI was performed in 139 oocytes. 34.5% had a normal fertilization with sperm. 25 (52.1%) embryos developed up to day 3, of which 11 (44%) had ≥6 cells. A single blastocyst was obtained on day 5 from the 1903 COCs. This technique resulted in a very low rate of successful embryo development.

SD: standard deviation.
NA: not applicable.
TGD: transgender and gender-diverse.
AFAB: assigned female at birth.
GAHT: gender-affirming hormone therapy.
IVM: in vitro maturation.
MII: Meiosis II.
COC: cumulus-oocyte complexes.

Table 8
Semen cryopreservation in transgender and gender-diverse adolescents assigned male at birth.

Authors, (year), country	Fertility preservation method	Study design	Study period	Sample size, population	Mean age ± SD/ median age (range) (years)	GAHT Mean length ±SD/ median length (range) (months)	Objectives	Outcomes
Adeleye et al. (2019) USA [106]	Semen cryopreservation	Retrospective cohort	2012–2018	N = 28 TGD AMABN = 18 with no prior GAHT use; N = 3 with prior use N = 7 current users	With no prior use 22.3 (18–27.6) with prior use 31.3 (23.4–39.9) current use of GAHT 28.9 [25.0 –30.1]	Length: 42 mean discontinuation:3, 6, 6.5; most used Estrogen and spironolactone	Semen quality parameters in TGD AMAB who pursued semen cryopreservation either in the presence or absence of GAHT.	Specimens collected in the presence of hormonal medication were associated with abnormal semen parameters. Specimens collected after discontinuation of GAHT were comparable to TGD AMAB who had never used GAHT.
Alford et al. (2020) USA [103]	Semen cryopreservation	Case report	NA	TGD AMAB adult	26	Estrogen injections and oral spironolactone 16 months.	Time to recovery for spermatogenesis after GAHT.	Recovery of semen after six weeks of cessation with a regimen of 75 units Follitropin Alfa (FSH) 3 times weekly and 25 mg oral clomiphene citrate (Clomid) daily. Successfully cryopreserved semen before SRS.
Amir et al. (2022) Israel [100]	Semen cryopreservation	Retrospective cohort study	2013–2020	N = 26 TGD AMAB adolescents and young adult	Mean age 16.2 ± 1.38	No	To determine the semen quality and cryopreservation outcomes among TGD AFAB adolescent before GAHT.	The median values of all semen parameters in our study group were significantly lower compared to the WHO data, including volume (1.46 mL vs. 3.2 mL) sperm concentration (28 × 106/mL vs. 64 × 106/mL) total sperm number (28.2 × 106 vs. 196 × 106), total motility (51.6% vs. 62%), and normal

								morphology (2% vs. 14%)
Barnard et al. (2019) USA [104]	Semen cryopreservation	Retrospective cohort study	2015–2018	N = 10 TGD AMAB adolescents and young adult	19.5 (16–24)	One person had treatment with leuprolide acetate. Second person had spironolactone and estradiol treatment. Both discontinued.	Study TGD adolescents after discontinuing GAHT to determine how cessation may change sperm quantity and quality.	The patient with prior GnRH agonist had normal sperm after 5 months. The patients with prior spironolactone and estradiol treatment had persistent azoospermia 2, 3, and 4 months up to orchiectomy. Patients with no prior GAHT had overall semen analysis parameters within normal limits expect from normal morphology.
Brik et al. (2019) The Netherlands [66]	Semen cryopreservation	Observational study	2011–2017	N = 35 TGD AMAB adolescents	14.8 ± 1.9	No	To examine the rate of attempted FP TGD AMAB adolescents who started GnRH agonist treatment.	The mean Tanner stage G5, range 4–5; testicular volume 17.2 mL. One was unable to ejaculate, one azoospermia, one severe oligozoospermia suitable for ICSI. Five adolescents stored ICSI four stored IUI quality.
Hamada et al. (2015) USA and Belgium [101]	Semen cryopreservation	Retrospective cohort study Two center	2003–2001	N = 2 TGD AMAB adolescents N = 27 TGD AMAB adults	17 and 18 years 28.4 1.1 (21–41)	No	Assess semen quality of TGD AMAB and evaluate adequacy for assisted reproduction technology.	A high frequency of impaired pre-freeze semen quality was observed. 25.9% had oligozoospermia, 33% had asthenozoospermia, and 25.9% had teratozoospermia. A low number of motile spermatozoa per ml were found in most samples (80%).
	Semen cryopreservation	Retrospective chart review	2010–2014	N = 9 TGD AMAB adults	28.5 (20–40)	6 patients had GAHT exposure and	Identifying the characteristics of this	The median concentration, motility

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Table 8 (*continued*)

Authors, (year), country	Fertility preservation method	Study design	Study period	Sample size, population	Mean age ± SD/ median age (range) (years)	GAHT Mean length ±SD/ median length (range) (months)	Objectives	Outcomes
Jones et al. (2016) USA [105]						discontinued for 0.33 months	patient population and the barriers to successful gamete banking.	and morphology is within the WHO reference of the general population. One patient used cryopreserved sperm with (ICSI) resulting in 1 pregnancy. Not mentioned if this patient used prior GAHT.
Li et al. (2018) UK [97]	Semen cryopreservation	Retrospective cohort study	2006–2016	N = 78 TGD AMAB adults matched with 141 healthy cisgender sperm bankers	24.1 ± 7.6 36.0 ± 9.4	No	Assess the incidence of sperm cryopreservation of transgender individuals compared with the cisgender population.	The TGD AMAB adults and adolescents demonstrated lower median sperm concentrations (14.2 vs. 19.2 × 106/mL), sperm count (55.7 vs. 69.5), TMSC (35.0 vs. 42.0), post-thaw sperm count (27.0 vs. 37.0), post-thaw motility (25.5% vs. 33.3%), and post-thaw TMSC (6.6 vs. 11.9) and also a higher incidence of oligozoospermia compared to cisgender men.
Marsh et al. (2019) USA [98]	Semen cryopreservation	Case-control study	NA	N = 22 TGD AMAB adults N = 17 Control fertile cisgender men who recently father a child.	26.70 ± 1.85 32.0 ± 1.04, respectively	No	Compare semen quality, hormonal status, and social factors in TGD AMAB adults seeking fertility preservation with those of fertile cisgender men.	The concentration of sperm was lower in TGD AMAB adults compared with fertile cisgender men. Semen from 3/22 transgender women was azoospermic. Total sperm and TMSC per ejaculate were lower in

								TGD AMB compared with fertile cisgender men.
Rodriguez-Wallberg et al. (2021) Sweden [99]	Semen cryopreservation	Prospective cohort study	2013–2018	N = 177 TGD AMAB adolescents and adults N = 16 previous used GAHT	Mean 24 (14–54) (IQR 20–28)	Length 12 (6–66) discontinued: 3 (1–5)	Assess sperm quality parameters of semen samples provided for FP by TGD AMAB people before or after (GAHT), and to compare sperm quality with a reference population of unscreened cisgender men defined by the WHO.	The median values for all sperm parameters were lower among TGD AMAB people who had received GAHT before FP compared to no GAHT, with statistically significant differences in sperm concentration and total sperm count. For TDG without prior GAHT total sperm count, sperm concentration, and sperm motility were significantly lower compared to the WHO reference.
Sermondade et al. (2021) France [102]	Semen cryopreservation	Retrospective cohort study	2018–2020	N = 83 TGD AMAB young adults N = 65 no prior GAHT, N = 5 previous GAHT N = 12 current GAHT.	With no prior GAHT 23.9 ± 0.6 With previous GAHT 27.2 ± 2.5 With current GAHT 30.8 ± 3.1	Lengths NA Discontinued for 3–6 months, Current GAHT consisted of estrogens combined with progesterone (n = 5), spironolactone (n = 1), or cyproterone acetate (n = 6).	Assess sperm quality parameters of semen samples provided for FP by TGD AMAB people before or after GAHT, and to compare sperm quality with cisgender sperm donors.	With no prior GAHT the main semen parameters, including semen volume, sperm concentration, progressive motility and vitality, were not statistically different between TGD AMAB and sperm donors. All semen parameters volume, concentration, motility and morphology were significantly altered in patients with current GAHT in comparison with those who never had GAHT. The finding of oligozoospermia and azoospermia was also more frequent. There

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Table 8 (*continued*)

Authors, (year), country	Fertility preservation method	Study design	Study period	Sample size, population	Mean age ± SD/ median age (range) (years)	GAHT Mean length ±SD/ median length (range) (months)	Objectives	Outcomes
								were no significant differences in the group who temporally stopped GAHT. All patients (n = 6) taking cyproterone acetate (alone or with estrogens) had azoospermia.
De Nie et al. (2020) The Netherlands [96]	Semen cryopreservation	Retrospective cohort study	1972–2017	N = 260 TGD AMAB >16 and older	24.0 years (IQR 20.0–29.5)	No	Semen quality in trans women at the time of fertility preservation, prior to the start of GAHT.	The median values of all semen parameters; volume 2.7 mL sperm concentration 40 million/ml, total sperm number 103 million and progressive motility 41% were significantly lower than the WHO reference. Only 26.4% of thawed semen samples was adequate for IUI. 21 had an azoospermia, three of these individuals reported to have used GAHT and stopped taking these 3 months prior to the first attempt. Six months after discontinuation of hormone treatment, they still remained azoospermic.

De Nie et al. (2022) The Netherlands [95]	Semen cryopreservation	Prospective cohort study	2018–2020	N = 113 TGD AMAB adults	24.1 (IQR 5.8)	No	Study the influence on semen quality in TGD AMAB at the time of fertility preservation.	Semen quality was significantly lower compared to the WHO reference. 60.2% had normozoospermic. Most thawed samples were only suitable for invasive techniques, such as IVF (9.6%) or ICSI (67.1%), and the post-thaw quality was suitable for IUI in only 23.3% of the samples.

SD: standard deviation.
NA: not applicable.
TGD: transgender and gender-diverse.
AMAB: assigned male at birth.
GAHT: gender-affirming hormone therapy.
FP: fertility preservation.
IUI: intrauterine insemination.
IVF: in vitro fertilization.
ICSI: intracytoplasmic sperm injection.
IQR: inter quartile range.

Table 9

Testicular sperm extraction and testicular tissue cryopreservation in transgender and gender-diverse adolescents AMAB.

Authors, (year), country	Fertility preservation method	Study design	Study period	Sample size, population	Age/Mean age ± SD	GAHT median length (range) (years)	Objectives	Outcomes
Joshi et al. (2021) USA [108]	Testicular tissue cryopreservation	Prospective research protocols	Since 2016	N = 4 TGD AMAB adolescents	10–16	NA	Safety of a pediatric ovarian and testicular cryopreservation program.	Successful testicular biopsy and testicular tissue cryopreservation including some mature sperm.
Parikh et al. (2021) USA [109]	Testicular tissue cryopreservation	Case report	2019	TGD AMAB adolescent with Tanner stage 3	13	No	Show fertility preservation options in adolescents prior to hormone treatment.	Pathology from the tissue biopsy showed the presence of five mature, live sperm, two motile, and three nonmotile. Twelve vials of testicular tissue were cryopreserved.
Peri et al. (2021) Australia [110]	Testicular tissue cryopreservation	Retrospective chart review	2013–2019	N = 31 TGD AMAB adolescents N = 25 without prior GAHT N = 6 with prior GAHT	13.4 (1.7) with no prior GAHT 14.5 years after GAHT	GnRH agonist for 1.5 (0.4–3.7)	Predicting successful sperm retrieval in after testicular biopsy.	68% were successfully able to store sperm before GAHT. The median total sperm count was 2.6 × 106 (IQR: 0.1–2 × 106/mL) and median % motile sperm was 0 (IQR: 0–2%). 32% had no sperm identified, and only testicular tissue was stored. Six patients had prior GAHT treatment.

								Only one patient had small numbers of mature, nonmotile spermatozoa ($<1 \times 105$) successfully isolated and frozen at the age of 15 having been on GnRH agonist more than 2 years.
Pang et al. (2020) Australia [64]	Testicular tissue cryopreservation	Retrospective chart review	2003–2017	N = 11 TGD AMAB	13.9 ± 1.5	7 prior to GnRH agonist 4 prior to GAHT 3 had prior GAHT	To examine FP use among TGD adolescents.	Five had mature sperm, six had germ cells cryopreserved.

SD: standard deviation.
NA: not applicable.
TGD: transgender and gender-diverse.
AMAB: assigned male at birth.
GAHT: gender-affirming hormone therapy.

that having biological children is important (9%–35.9%) [35–38,41]. At the time of study, adolescents were most interested in adoption ranging from 70% to 80% [35,36,42].

The most common barriers for a desire for children were discomfort with a body part they do not identify with, delaying GAHT and financial considerations [41], stress to think about having a child one day, and delaying or stopping transition and time and effort to have a child [42].

Desire for children in transgender and gender-diverse adults

The desire for children in TGD adults was described in 12 articles (Table 2). Nine studies reported on the desire for children in Europe, the US, or Australia [43–51], and three studies were conducted in Turkey, Thailand, and Mexico [52–54]. Three studies included data on barriers to fulfill their parental desire. Seven studies included both AFAB and AMAB TGD adults, two studies included AFAB TGD adults [46,49], and two studies included AMAB TGD adults [48,53].

Four studies showed that the majority of the TGD adults have a desire for children ranging from 54% to 82% [43,45,46,55]. However, a minority of participants (37% AFAB and 50% AMAB) preferred biological offspring [43].

In a German cohort of 189 TGD adults by Auer et al. the future desire for children was evaluated between a group prior to GAHT and a group during GAHT. AMAB people showed no significant difference between both groups (65.4% prior to GAHT vs. 69.9% during GAHT), whereas AFAB people showed a significantly lower desire for children after transition (53% prior to GAHT vs. 46.9% during GAHT, $P = 0.049$). In both groups, most people reported adoption to be the most desirable parenting option [47].

In a cohort of 254 nonclinical AMAB TGD adults [48], 22.5% had reported a current or future parental desire, 32.9% already fulfilled their parental desire, and the parental desire was nonexistent in 22.1%. In the same nonclinical cohort of 172 AFAB TGD adults [49], 39.0% of the respondents had a current/future parental desire, parental desire was already fulfilled in 9.3%, and nonexistent in 39.0%. The two most reported barriers to fulfill their parental desire for both AMAB and AFAB were fear of their child being discriminated due to having TGD parents and the assumed difficulties with the adoption procedure [48,49].

In an Australian cohort of 114 TGD adults, 18.4% reported a desire for children, and 52.6% stated they did not want to become parent. Participants who felt more supported were more likely to place importance on having children in the future [51]. Another Australian study compared TGD adults with and without children. Thirty three percent of the group without children desired to have children in the future compared to 18.8% of participants who are already parenting children. In both groups, 33.6% found that biological relation was important [50].

In a cohort of 171 TGD adults in Turkey, they found a similar desire for children compared with a matched cisgender control group [52]. In a cohort of 303 TGD AMAB adults in Thailand, 30.4% had a desire to become a parent, and almost half thought that a genetic relation is important. Barriers to become a parent were no acceptance by society (19.1%), afraid their gender identity may affect a child's well-being (28.7%), fear their financial status is not good enough to raise a child (25.7%), difficult medical processes (14.5%), and 5.3% felt that it is was illegal [53]. In a Mexican study in 2015, 36% had parenting aspirations and 25% were unsure [54].

Parenthood in transgender and gender-diverse people

Six studies reported about parenthood and the way to parenthood in TGD adults (see Tables 2 and 4). Between 16% and 30% of the TGD adults were currently parenting children [47,50,51,56]. The majority of participants became parents before they started their transition (59–100%) [47,50]. The majority of the TGD partners gave birth [47,50,51]. However, some TGD people gave birth themselves, including after gender transition [46,51]. The minority became a parent through adoption or foster care [46,50]. In a Brazilian cohort, 6.6% of the TGD were parents and most through biological means. TGD parents report more discrimination, and 17% reported having lost or having the custody reduced for being TGD, and 48% suspected or were told their ability to see their children less was due to their gender identity [57].

Part 2: Fertility counseling and utilization

Fertility preservation in transgender and gender-diverse adolescents

Eleven studies reported whether TGD adolescents received FP counseling (see Table 3). In all studies, the large majority of the adolescents had received FP counseling ranging from 88% to 100% [36,58–64], with the exception of two studies who reported a low FP counseling rate; Chen et al. showed only 13.5% self-reported FP counseling [35], and Komorowski et al. showed 50% documented FP counseling [38].

Only a small percentage desired a referral to a fertility specialist for counseling (12.4–24%) [58,62,63] and even less eventually pursued FP ranging from 16% to 0% [36,38,40,59,60,62,63,65]. In all studies, more AMAB TGD adolescents completed FP compared to AFAB TGD adolescents. Only one study from the Netherlands reported high FP utilization, 91% of AMAB TGD adolescents received FP counseling, and 38% attempted FP [66]. In the Netherlands, FP is insured for all TGD people, which may explain these higher percentages.

Reasons for declining FP were not wanting (biological) children, preference to adopt, the cost, seeing themselves as too young, not wanting to delay GAHT, invasiveness of procedures, and feeling uncomfortable with masturbation [40,58,60,61]. However, some AFAB adolescents will consider FP in the future [64].

Fertility preservation counseling and utilization in transgender and gender-diverse adults

Thirteen studies reported on FP counseling, FP utilization, and barriers around FP for TGD adults (see Table 4). In all studies, FP utilization consisted of semen cryopreservation or oocyte cryopreservation.

Four studies showed a low FP counseling rate; in these studies, the FP utilization rates are also low (8.7–15.8%). In the countries where FP is covered by insurance, almost all participants received FP counseling, and the FP utilization rate was higher as well (5.8–85.7%) [43,55,67,68].

Four studies reported that 50–66% received FP counseling [45,48,49,69]. FP utilization differed between countries where FP is covered by insurance and between assigned sex at birth. In countries where self-pay was necessary, FP utilization rates ranged from 3% to 16% [47–50,53,56,69,70], with higher FP utilization rates in people AMAB in all studies. In countries where there were less financial barriers, the FP utilization rates ranged from 6% to 76% [43,44,67,68]. However, the studies from Mattelin et al. and Eustache et al. reported the FP utilization from the people who were referred for FP after receiving FP counseling. Eustache et al. stated that looking at the self-reported prevalence of TGD people in the general population, the FP utilization rate was still low. Again, there was a higher FP utilization rate among AMAB people. In Israel, FP is only insured for people AMAB, which may explain the large gap between AMAB and AFAB people.

More TGD adults are willing or thinking about banking their gametes than the FP utilization rates show. In the UK, 20.1% wanted to bank gametes versus 4.4% who actually did [70] because the majority could not afford it. In Germany, where oocyte donation is illegal, 76.6% of participants thought about oocyte vitrification [47]. In Belgium, 37.5% would have considered FP if it was available at the time of medical transition [46], as well as 25% in Thailand [53]. In Turkey, where GAS for legal gender affirmation is still needed and FP is illegal for TGD people, 50% AMAB and 17.4% AFAB regretted not pursuing FP after GAS [52].

The reported barriers to pursue FP for both AMAB and AFAB were not wanting (biological) children, not wanting to delay starting GAHT, the expenses and invasiveness of the procedures, potential worsening of gender dysphoria, and concern over the attitude of medical staff [43,45,48,49,70]. For AMAB adults, masturbation to produce a sperm sample was the main reported barrier. For AFAB adults, the fear of gender dysphoria caused by the hormonal treatment, distress caused by the FP technique (internal examination), and the chance of successful conception from frozen oocytes were the main barriers.

Part 3: Fertility preservation options and outcomes

Oocyte and embryo cryopreservation in transgender and gender-diverse people assigned female at birth

Oocyte cryopreservation includes controlled ovarian hyperstimulation and oocyte retrieval for mature metaphase-II (MII) oocyte vitrification. When semen is available, either from a partner or donor, the mature oocyte may be fertilized with semen for embryo vitrification. Oocyte and embryo cryopreservation is used to preserve fertility by freezing gametes or embryos for potential future use. An embryo may be transferred to the uterus of the TGD person themselves, their partner, or gestational carrier. Seventeen studies reported successful cryopreservation in TGD adults and adolescents (see Table 5). Four studies compared mature oocyte retrieval outcomes between TGD AFAB adults matched with cisgender women [71–74], and one study described outcomes in TGD AFAB adolescents [75]. All five studies found no differences in the number of retrieved mature oocytes. Additionally, Israeli et al. found no difference in the development and quality of embryos from testosterone-exposed TGD people compared to cisgender women [73]. Furthermore, four studies reported successful pregnancies and life births with embryos used from testosterone-exposed TGD people (n = 12) [71,74,76,77]. After 11 months of follow-up, the infants were doing well [77]. There were no studies reporting on the long-term outcomes of the children.

Two studies compared ovarian stimulation outcome between TGD AFAB patients with and without prior testosterone use. One study by Adeleye et al. found a lower oocytes retrieval outcome between TGD patients with prior testosterone use [71]. Although another study by Amir et al. found no difference in the number of oocytes retrieved at ovum pickup [72].

The remaining ten studies are case reports or case series. Seven case reports showed successful oocyte cryopreservation in TGD AFAB adults [76–82]. Four of these studies showed the feasibility of oocyte cryopreservation without discontinuation of testosterone, and all showed a successful mature oocyte cryopreservation [78,79,81,82]. Strikingly, Greenwald et al. also reported a live birth after embryo transfer to a partners' uterus from one of these testosterone-exposed oocytes.

Five case reports or case series showed successful oocyte cryopreservation in TGD AFAB adolescents and young adults [83–87]. Including two participants previously on PS with a GnRH agonist [86,87].

Pregnancy in transgender and gender-diverse adults assigned female at birth

For some TGD AFAB people, carrying a pregnancy is the preferred or the only way to fulfill their desire for biological children. Seven studies reported on pregnancy in TGD AFAB people (see Table 6). In a large population-based cohort study, researchers found that 498 registered fathers gave birth in the state of California (the US). They found no significant differences in obstetrical and birth outcomes compared to heterosexual ciswomen opposite to bisexual ciswomen. However, prior or current testosterone use was not specified in this study [20]. In an online questionnaire study in the US, 12% of the 1694 TGD AFAB people reported ever being pregnant, resulting in 169 live births (39%), 142 miscarriages (33%), and 92 abortions (21%). Twelve respondents used testosterone prior to their pregnancy, and 3 respondents were pregnant while using testosterone, resulting in a miscarriage or abortion [88]. In a cohort of 41 TGD AFAB people, 25 used testosterone before conceiving, and 20% used testosterone for more than 10 years. All conceived between 1 and 6 months after the cessation of testosterone. Pregnancy, delivery, and birth outcomes did not differ in relation to prior testosterone use [89]. Three case reports showed a successful live birth after prior testosterone use [90–92] and showed no developmental abnormalities in the child after a 3 year follow-up [91].

Ovarian tissue cryopreservation and in vitro maturation in transgender and gender-diverse people assigned female at birth

Some TGD AFAB adults are not able to undergo ovarian hyperstimulation due to increasing gender dysphoria triggered by internal examinations, hormone injections, and bleeding. Ovarian cortex cryopreservation or the collection of immature oocytes at the time of GAS may be an alternative option for fertility preservation. Autologous transplantation of cryopreserved ovarian tissue is already successfully applied in oncological patients. For TGD people, autologous transplantation may not be the most feasible option as dysphoria toward the female reproductive organs is often the reason for gonadectomy. Therefore, many TGD people pursuing ovarian tissue cryopreservation depend on in vitro maturation (IVM) and ART. Currently, IVM from a primordial follicle is still considered experimental due to limitations of the culture procedure. So far, three studies evaluated the option of IVM in TGD people (see Table 7). From the medulla of the cortex, cumulus-oocyte complexes (COC) are retrieved, and an IVM process is performed. Theoretically, all mature oocytes in MII with a normal spindle structures and chromosome alignment are cryopreserved, after thawing fertilization through intracytoplasmic sperm injection (ICSI) is performed to achieve embryo development. Two studies showed an IVM fertilization rate between 34 and 38% and after vitrification [24,93]. Lierman et al. found a normal spindle structure and chromosome alignment after warming [93]. However, there was a very unsuccessful embryo development; they created 1 blastocyst out of the 1903 COC, retrieved from 83 TGD adults, 5 days after fertilization through ICSI [94]. In summary, IVM has not been successful yet. For the majority of TGD people, autologous transplantation is not desired but may be the only way ovarian cryotissue is useable for them.

Semen cryopreservation in transgender and gender-diverse adolescents assigned male at birth

TGD postpubertal adolescents and adults AMAB may produce a semen sample through masturbation or assisted ejaculation, e.g., electroejaculation or penile vibratory stimulation. The obtained spermatozoa are cryopreserved for potential future use. Sperm may be used for conception with a partner or gestational carrier. Depending on the quantity and thawed sperm quality, the type of ART treatment is determined. Analyzing the quality, semen is tested for the number of spermatozoa, sperm concentration, ejaculate volume, and sperm morphology. The sperm motility or the total motile sperm count (TMSC) is calculated by volume [mL] x concentration [sperm cells/mL] x percentage of progressive motile cells.

Thirteen studies reported on the semen quality of TGD AMAB people (see Table 8). Eight studies included only TGD AMAB people prior to hormone treatment [61,95–101].

Semen quality from TGD AMAB adults and adolescents was significantly lower compared with the WHO standard for the general population [95,96,99,100]. In both studies by de Nie et al. merely one-fourth of the post-thawed semen samples were suitable for IUI [95,96].

Three studies compared semen quality with a matched cisgender control group [97,98,102]. Two studies showed lower semen quality in TGD adults and adolescents compared with the cisgender control groups [97,98]. One cohort of 83 TGD people compared sperm samples of TGD people with and without prior GAHT to a cisgender control group [102]. They found no statistically significant difference between TGD AMAB adults with and without prior GAHT compared with cisgender sperm donors. Although all semen parameters were significantly lower in the group currently on GAHT.

Four studies reported previous use of GAHT when pursuing semen cryopreservation [99,103–105]. Two studies included 19 TGD AMAB people currently using GAHT [102,106]. The study by Sermondade et al. reported that all semen parameters were abnormal in patients using estrogens only or combined with spironolactone (n = 6), and all patients using estrogen and cyproterone acetate had an azoospermia (n = 6). In the study by Adeleye et al. all patients using estrogen and spironolactone had an azoospermia (n = 3) or were suitable for IUI/IVF (n = 3) or ICSI (n = 1). In both studies, the quality of semen specimens collected after discontinuation of GAHT was comparable to TGD AMAB who had never used GAHT. The mean discontinuation of GAHT ranged from 3 to 6.5 months [102,106].

Four other studies also reported on the sperm quality after discontinuing GAHT. In a cohort of six patients, all had successful cryopreservation after a median 0.33 months on GAHT, of unknown type of GAHT and semen quality [105]. One case showed an 18-year-old with 6 months' prior use of GnRH agonist who had normal sperm after 5 months of discontinuation. A second case report showed a 19-year-old with 26 months prior use of spironolactone and estradiol treatment and had a persistent azoospermia after 2, 3, and 4 months and never successful cryopreserved their semen before gonadectomy [104]. Another case report showed a successful recovery of semen quality after only six weeks of cessation estrogen and spironolactone GAHT with a regimen of 75 units Follitropin Alfa (FSH) 3 times weekly and 25 mg oral clomiphene citrate (Clomid) daily [103].

The etiology of impaired semen quality prior to GAHT, or after GAHT cessation, remains largely unknown. A study by de Nie et al. showed behavioral factors, including wearing tight undergarments and extensive tucking, may contribute to lower semen quality. However, not all abnormalities were declared by demographic factors, lifestyle or behavioral factors, or medical history [95].

Testicular sperm extraction and testicular tissue cryopreservation in transgender and gender-diverse adolescents assigned male at birth

Testicular sperm extraction (TESE) may be a suitable option for TGD AMAB adolescents who are not able to ejaculate due to not being biologically or mentally mature enough yet. But also for TGD AMAB adults experiencing too much gender dysphoria during masturbation, or who have a nonobstructive azoospermia, but do desire sperm banking. Via a small surgical procedure, any viable sperm is isolated from testicular tissue and cryopreserved. TESE is currently widely used in people with a nonobstructive azoospermia and is also offered to pediatric oncological patients for fertility preservation. When no mature spermatozoa are found, spermatogonial stem cells in the testicular tissue may be cryopreserved, which is currently studied in oncological prepubertal patients. However, the use of spermatogonial stem cells remains experimental. In contrast to ovarian tissue, testicular tissue cryopreservation at the time of GAS for autologous transplantation has only been successful in animal studies [107]. Furthermore, IVM of spermatogonial stem cells or cryopreserved testicular tissue has not been successful in humans or animals.

Four studies described a TESE in TGD AMAB adolescents [108–110](see Table 9). One retrospective study showed 68% successful TESE of mature spermatozoa in 31 adolescents. They found that TESE was most successful when the testicular volume was $\geq$10 mL. Only one of the six patients currently using PS had mature spermatozoa in their testicular biopsy [110]. The same research group previously described 11 TESEs, of which 5 were mature spermatozoa and 6 were only germ cells, which were also cryopreserved [64]. One prospective study enrolled adolescents with fertility-threatening conditions for testicular tissue cryopreservation, including 4 TGD adolescents. Three of them had mature spermatozoa and were Tanner stages 1, 3, and 4 at the time of TESE. One adolescent had no mature spermatozoa and was Tanner stage 2 [108]. One case report showed successful TESE of 5 mature spermatozoa in a 13-year-old Tanner stage 3 and cryopreserved the rest of the tissue [109].

Discussion

Main findings

In this systematic review, we aimed to report on (1) desire for children and parenthood, (2) fertility counseling and utilization, and (3) fertility preservation options and outcomes in TGD people. In the first part, we showed that more than 50% of adolescents and adults expressed a desire for (future) parenthood [35–38,43–46], but biological offspring was not the preferred option for most [35–38,41,43,50]. In the second part, we showed a varying percentage of TGD people receiving FP counseling, where in most studies the percentage was >50%. There was an overall low FP utilization rate, with the lowest rate in countries with no insurance and in people AFAB. In the third part, we showed several options for FP and their outcomes. The most used FP strategies include oocyte vitrification and sperm banking through masturbation. Oocyte vitrification in TGD people AFAB during or after testosterone cessation showed comparable outcomes to cisgender people and TGD people who have not yet started GAHT. Sperm analyses when banking sperm in TGD people AMAB prior to GAHT showed lower semen parameters compared to cisgender controls. When on GAHT, there is likely no spermatogenesis, and after cessation this remains unclear. FP strategies using ovarian cryopreserved tissue for autotransplantation are currently only applied in oncological fertility; for testicular cryopreserved tissue, this is even more experimental. For both, TGD people depend on the future development of successful IVM techniques.

This review showed that the majority of TGD adults and adolescents have a desire for children, but biological relatedness is less important. For TGD people, fulfilling a desire for children comes with a lot of barriers, and pursuing biological offspring comes with even more barriers [41,42,48,49,53]. Most TGD adolescents who report a future desire for children prefer adoption over biological offspring [35,36,42]. However, looking at parenthood in TGD parents, more people are currently biological parents [46,50]. Adoption is a long and complicated journey because of financial and legal challenges. For these reasons, adoption may not be the most realistic option for most TGD adolescents when they reach adulthood.

In contrast to several transgender health guidelines [28,30,111], we found that FP counseling is not provided as standardized care everywhere [45,48,49,69]. Furthermore, FP utilization rates are not in line with TGD people's desire for biological children. Relatively more TGD adolescents received FP counseling compared to TGD adults, still the number of adolescents who pursued FP remained low

[36,58–62]. As suspected, in countries where FP is covered by insurance, the counseling rates were higher and more TGD people pursued FP. This suggests the cost of FP is a great barrier for TGD people to pursue FP. We also saw a higher FP utilization rate for AMAB people compared with people AFAB [47–50,53,56,69,70]. This may be because sperm banking via masturbation is significantly cheaper and medically less invasive compared to ovarian hyperstimulation for oocyte cryopreservation.

Strengths and limitations

This review is a complete and comprehensive systematic overview of available evidence on parenthood and fertility preservation in TGD people. We included a total of 76 articles, 59 cohort studies describing TGD adults and adolescents, with a range of 20 up to 3667 persons per cohort), and 17 case reports and small case series. The studies were conducted in 16 different countries, mostly from Europe and the US. The majority of the studies were conducted in the US (35 out of 76). Research in the field of reproductive health in TGD persons is growing almost exponentially. More than half of the papers in this SR were from the year 2020 onward (41 out of 76). This systematic review complements the last systematic review of Baram et al. published in 2019 [112].

The main limitation of this systematic review is the low-quality body of evidence presented. Even though we included many studies, most were cross-sectional questionnaires, case series, or small sample size cohort studies with limited follow-up time and lack of control groups. Furthermore, the quality assessment of the included studies was low to moderate. Interpretation of this evidence requires caution; however, it is the best available data at this time.

Due to the methodological set-up, small sample size, and high heterogeneity of the included studies, we were unable to examine the presence of publication or reporting bias. Furthermore, we were unable to pool results or perform a meta-analysis.

Clinical implications

We state that it is not medically necessary for AFAB TGD people to pursue FP before the start of PS or affirming hormones if they are willing to temporarily discontinue testosterone in the future. Studies reporting on oocyte vitrification outcomes showed no difference in outcomes between TGD people who pursued oocyte cryopreservation prior to or after starting testosterone even after long-term testosterone exposure of more than 10 years (ranging from 10 to 17 years) [67,73,74]. Although there are no long-term follow-up studies of children born after oocyte cryopreservation with prior GAHT use.

The timing of oocyte cryopreservation depends on someone's personal preference, reproductive age, and desire for GAS. Keeping in mind that oocyte vitrification is no longer an option after gonadectomy and a more advanced oocyte age negatively impacts oocyte cryopreservation outcome [113].

For oocyte cryopreservation, we suggest a short period of cessation of testosterone, with a lack of evidence ~3 months (time of full oocyte maturation). As testosterone cessation can be quite burdensome because of the return of monthly blood loss, cycle regulation may be established by the temporary use of a GnRH agonist or progesterone.

In contrast to AFAB TGD people, we strongly advice to pursue FP before starting GAHT for AMAB people who desire FP. Semen parameters while using GAHT are most often abnormal and show azoospermia [102,106]. After discontinuing GAHT, it remains unclear if and when the spermatogenesis will recover [99,104].

We advise AMAB adolescents who desire FP to consider pursuing this prior to the start of PS. Even though delaying these blockers may result in (further) the development of the secondary sex characteristics and subsequent gender dysphoria, we also know that almost all adolescents continue with GAHT after suppression [114]. Hence, the spermatogenesis may never develop, as we have seen in histology samples of TGD people who started PS in Tanner stage 2 or 3 during GAS who solely show spermatogonial stem cells at surgery [14]. A TESE may be a suitable option for young adolescents who are a bit further in puberty development (Tanner 4–5, with testicular volume >10 mL) but unable to ejaculate. However, further research needs to be done concerning the optimal timing and the impact of TESE for these adolescents.

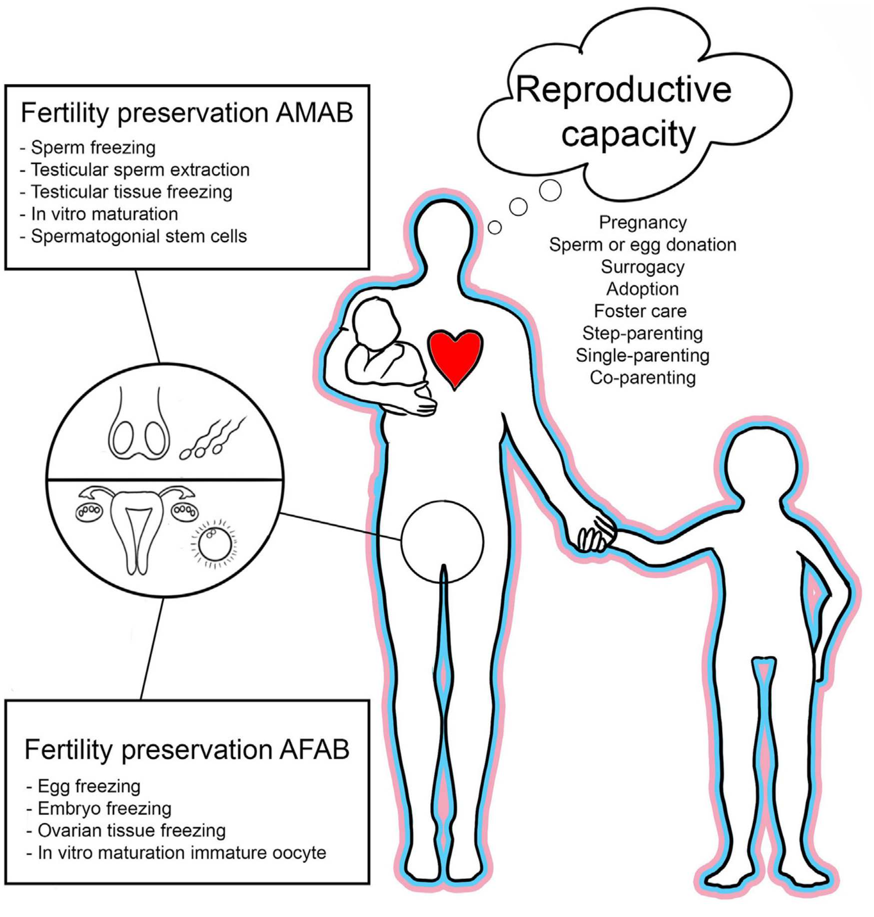

Fig. 2. Journey to parenthood.
Subscript: The journey to parenthood is related to the mental reproductive capacity of TGD people, which is dependent on the sexual attraction and the gametes they are born with. If biological offspring is desired, AFAB people can carry a pregnancy and both AFAB and AMAB people can use various fertility preservation techniques (shown on the left side in the figure). If biological offspring is not desired, multiple options are available depending on one's personal preferences (shown on the right side in the figure). The sexual attraction and one's partner may influence these decisions as they come with their own set of gametes and reproductive desires.

Future perspectives

To improve oocyte vitrification treatment, continuing testosterone needs to be studied further as this may be a strong barrier or even a reason to refrain oocyte cryopreservation for some TGD people. Data on oocyte vitrification while continuing testosterone are limited ($n = 3$); therefore, evidence-based recommendations cannot be made [80,82,83]. Another research topic that could make the ovarian hyperstimulation more bearable is the use of aromatase inhibitors to keep the estrogen levels lower during stimulation. Data on including an aromatase inhibitor to the ovarian stimulation protocol, while sometimes utilized in oncological fertility preservation [114], have only been described in TGD people once [88].

To improve sperm banking for those who want to bank sperm after initiating GAHT, an interesting addition may be the use of FSH and clomiphene citrate for a more rapid recovery of the spermatogenesis [103].

Ovarian and testicular tissue cryopreservation

Future research on ovarian cryopreservation and IVM is necessary. However, ovarian tissue cryopreservation could already be offered at the time of GAS. Because autologous transplantation has already been proven successfully for cisgender female oncology patients [115], some AFAB TGD people may choose this option in the future if their desire for children develops in the absence of IVM strategies at that time.

For TGD AMAB in whom freezing of spermatozoa is not possible, testicular tissue cryopreservation may seem a promising option as fertility loss is permanent after gonadectomy at the time of GAS. In contrast to ovarian tissue, autologous transplantation with testicular tissue or spermatogonial stem cells has only been successful in one animal study [107]. Furthermore, autotransplantation of testicular tissue or spermatogonial stem cells is no longer possible following orchiectomy, and therefore TGD people rely solely on IVM after GAS. Therefore, further research on testicular tissue cryopreservation and IVM is necessary. This technique might also be applied to adolescents who do not want to postpone PS or GAHT and are still in early Tanner stages. Cryopreservation of testicular tissue is already advised for pediatric oncology patients [116] even when it is not certain if they become infertile due to the chemo or radiotherapy.

Uterus transplantation

TGD AMAB people have a stronger desire to carry their own pregnancy compared to the insemination of a cisfemale partner or surrogacy using their own sperm [117]. To fulfill this desire for TGD AMAB people, a uterus transplantation may be an interesting future perspective. Since 2000, uterus transplantations have been carried out in cisgender women with uterine factor infertility, with a reported live birth rate of 40 children [118]. The donor could be either deceased or alive. Some suggest TGD AFAB people may be suitable life donors if they are willing to donate their uterus at the time of GAS [119]. However, the morbidity of the donor procedure is much higher compared to a gender-affirming hysterectomy, i.e., longer surgery time, more elaborate surgery, and higher complication risks [118]. Of the first 80 uterus transplantations until 2021, 18% needed a second surgery because of complications. Even after explaining these risk factors, a high percentage of TGD AFAB people are still open to donation (97% before counseling vs. 84% after counseling risk factors) [119]. In addition to ethical and medical considerations, the cost of uterus transplantation is a major barrier. A Dutch study estimated the costs at 100.000 euros, which would not be covered by the health insurance [120].

Gamete uptake after fertility preservation

Very little is known about the use of gametes after sperm of oocyte cryopreservation; only case reports or small case series have published these results [76,105]. One study by Mattelin et al. received 3 requests at the time of the study (oocyte n = 1/43 and sperm n = 2/53) [55]. An explanation for a low gamete uptake may be the challenge to find a partner or gestational carrier who is able to carry the pregnancy because a pregnancy through oocyte donation comes with greater risks and costs, and in some countries it is still illegal. Another explanation for the low uptake of frozen gametes may be the young age of TGD people at the time of FP. Perhaps they do not have an active desire for children yet. In this case, it is likely that fertility clinics may see an increase in requests for the use of banked gametes in the following years. Uptake requests should be registered and investigated in the future to reach a complete picture of reproductive health in TGD people. However, even in the oncological population, where more long-term follow-up is available, the FP uptake rate remains below 10% [121,122]. Those who are critical toward fertility preservation in TGD people may use the low uptake rate in TGD as an argument against FP, while there is no discussion about the meaningfulness of FP for cancer patients and their uptake after recovering [123,124]. Another understudied part is the effect of FP on the quality of life and the reduction in stress in TGD people who pursued FP and may be another outcome to investigate next when concerning the usage of stored gametes.

Conclusion

The majority of TGD people have a desire for children. Therefore, it is of utmost importance that all TGD people have access to fertility counseling and preservation prior to PS, GAHT, and GAS. The journey to parenthood may depend on different values and considerations compared to cisgender people. We state that the journey to parenthood is related to the mental reproductive capacity of TGD people, their sexual attraction, and the gametes they are born with (summarized in Fig. 2). The reproductive capacity determines the route to parenthood (e.g., biological or nonbiological parenthood) depending on someone's sexual attraction and available gametes, either fresh or frozen. The journey to parenthood presents lots of barriers for TGD people. For example, laws that prohibit ART, adoption, or surrogacy for TGD people. Most laws are based on concerns that TGD parenthood may be harmful to the development of their children. However, in this review, we found no evidence for these concerns. Future research needs to focus on long-term follow-up and outcomes of children born after using hormone-exposed gametes and experimental techniques to help global acceptance by society regarding TGD parenthood, expand accessibility in healthcare, and eliminate anti-TGD parenthood legislation.

Practice points

- Fertility counseling is paramount prior to gender-affirming care.
- A desire for children may change over time; therefore, we recommended to repeat fertility counseling over time as well.
- For transgender and gender-diverse people assigned male at birth to pursue sperm banking prior to puberty suppressants or gender-affirming hormone therapy if they desire fertility preservation.
- For transgender and gender-diverse people assigned female at birth to pursue oocyte vitrification depending on their preferences. It is not medically necessary to pursue oocyte vitrification prior to puberty suppressants or gender-affirming hormone therapy as they can most likely also pursue this at a later age if they are willing to temporarily discontinue testosterone at that time.
- Provide access to fertility services and insurance coverage for fertility services for TGD people.

Research agenda

- Children's health outcome when born from gender-affirming hormone treatment-exposed gametes.
- Oocyte vitrification without the cessation of testosterone.
- Addition of aromatase inhibitors to an ovarian hyperstimulation protocol in oocyte vitrification treatment.
- Examine the role of gonadotropins stimulation protocols to reduce the time to spermatogenesis in TGD assigned male at birth people after gender-affirming hormone therapy cessation.
- Timing and burden of testicular sperm extraction of TGD adolescents assigned male at birth.
- In vitro maturation of primordial follicles and spermatogonial stem cells.

Declaration of competing interest

The authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2023.102312.

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