1-1-2018

Reproductive Health And Fertility Among Transgender Adolescents: A Knowledge And Attitudes Survey

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A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

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2018

Abstract

The goal of this study was to determine the knowledge and attitudes of transgender adolescents regarding fertility and future parenthood. We developed and administered a cross-sectional questionnaire to a convenience sample of 23 transgender and gender non-conforming adolescents (mean age 16.2 ± 2.6) who attended the Yale Pediatric Gender Program between October 2016 and August 2017. Our results indicate that transgender adolescents have a basic understanding of reproductive health and fertility (mean total knowledge score of 3.78 ± 0.80 out of 5). Knowledge scores were significantly higher in participants with previous information about gender-affirming hormone therapy (GAH; $p<0.05$), which most commonly came from a physician (65%). When asked about future parenthood, most participants favored non-biological over biological parenthood (70% vs. 22%). Similar proportions of participants viewed future parenthood as important and unimportant (both 30%), but those who reported future parenthood as the least important had the greatest level of concern about becoming a parent ($p<0.0001$). Other common concerns included the postponement of GAH to preserve fertility (35%) and the time and effort required to have a child (30%). Outcomes did not differ significantly by use of pubertal blockers or GAH. In conclusion, transgender adolescents at our university-based clinic are overall knowledgeable about reproductive health and fertility and favor non-biological parenthood. Patient education by providers effectively increases knowledge and awareness of transgender-specific fertility topics. Despite this, many still disclose concerns and may express these concerns as disinterest in parenthood. This data highlights the need for frequent and repeated counseling with every patient about the risks for diminished fertility with GAH and options for future parenthood. Doing so will enable transgender adolescents to make reproductive-related decisions based on careful consideration rather than fear or concern.

Acknowledgements

First and foremost, I would like to express my sincere gratitude to Drs. Julia Cron, Amanda Kallen, and Christy Olezeski. Thank you for trusting me to do this project and for your unwavering support of my thesis work and career goals. I am inspired by your commitment to your patients and the profession and feel honored to have benefited from your extensive personal and professional guidance. I would also like to thank Dr. Anisha Patel, Dr. Susan Boulware, Dr. Stuart Weinzimer, Faria Kamal, Wendy Bamatter, Rachel Lawton, and everyone at the Yale Gender Program (YGP) who provided feedback and support for this survey project. You truly embody what it means to provide inclusive, compassionate patient care. Thank you to the patients at the YGP. You are at the heart of this project, and I will be forever grateful that you took time to share your thoughts about such intimate topics with me. To Fritha Morrison, thank you for spending countless hours explaining statistics to me. Maybe one day I will be able to understand it on my own, but until then I am grateful to have you. I am also thankful to the Yale Office of Student Research for financial support. Deepest thank you to my family and friends—Peter and Effie Alphonso, Nicolette and Denby Morrison, Catherine Tomasulo, Aman Shah, and Anna Diakun—who have loved and supported me unconditionally throughout this journey through medical school. Finally, but by no means least, I sincerely thank my husband Lliam Morrison. There are no words.

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List of Abbreviations

ART	assisted reproductive technology
DSM	Diagnostic and Statistical Manual of Mental Disorders
FP	fertility preservation
FtM	female-to-male; also known as transgender male
GAH	gender-affirming hormone therapy; formerly referred to as cross-hormone therapy or cross-sex hormone therapy
GnRHa	gonadotropin-releasing hormone agonist
ICSI	intracytoplasmic sperm injection
IUI	intrauterine insemination
IVF	in-vitro fertilization
MtF	male-to-female; also known as transgender female
OTC	ovarian tissue cryopreservation
TESE	testicular sperm extraction
WPATH	World Professional Association for Transgender Health
YGP	Yale Pediatric Gender Program

1 Introduction

1.1 Background

As many as 1.4 million people in the United States identify as transgender, or have a sex assigned at birth that is incongruent with the internal gender with which they identify (1). In some transgender individuals, this incongruence causes an intense and pervasive sense of distress or discomfort known as gender dysphoria. Transgender individuals with gender dysphoria are two to four times more likely to have been diagnosed with depression, anxiety, and suicidal ideation than the non-gender dysphoric population (2–4). A large national transgender survey found that 41% of transgender adults have ever attempted suicide, over 25 times the 1.6% suicide attempt rate in the general population (5). These findings provide a strong impetus to examine the healthcare needs of transgender individuals and to provide high-quality, gender-affirming care.

At present, the treatment options available for alleviation of gender dysphoria include medical therapy and surgery. Transgender individuals may utilize one, both, or neither of these options in the course of their transition. Two forms of medical therapy used to alleviate gender dysphoria are (1) puberty blocking medication to prevent the development of unwanted secondary sex characteristics and (2) masculinizing or feminizing hormones to facilitate gender transition. Children as young as age eight who are entering puberty and experiencing gender dysphoria may delay puberty through the use of gonadotropin-releasing hormone agonists (GnRHa), the most common type of puberty blocking medication (6). GnRHa are synthetic hormones that mimic the action of naturally occurring GnRH, which stimulates the downstream production of the sex hormones estrogen and testosterone with pulsatile administration but suppresses or “shuts

down" the production of these hormones with sustained, non-pulsatile administration. Older adolescents and adults may seek gender-affirming hormone therapy (GAH)[1] through the masculinizing hormone testosterone or the feminizing hormone 17β-estradiol (7). Testosterone facilitates the female-to-male transition by stimulating androgen receptors, causing a deepened voice, male pattern facial and body hair development, and increased muscle mass (8,9). 17β-estradiol is a form of estrogen which facilitates male-to-female transition by stimulating estrogen receptors in the testes and breasts, causing decreased testicular size and breast growth (8). GAH is typically started after age 16, but may be started as early as age 13.5 to 14 in adolescents who are well-established in their gender identity (10–12). GAH is the primary medical therapy pursued by transgender individuals to attain secondary sex characteristics better aligned with their gender identity.

Gender-affirming surgery includes many options such as gonadectomy—removal of the ovaries or testes; hysterectomy—removal of the uterus; chest surgery ('top surgery')—masculinizing through the removal of breast tissue or feminizing through the placement of breast-shaped implants; genital surgery ('bottom surgery')—masculinizing phalloplasty to create a penis or feminizing vaginoplasty to create a vagina; facial feminization surgery to create a feminine facial profile; among others. According to guidelines from the World Professional Association for Transgender Health (WPATH), transgender individuals older than 18 years who have been on hormonal therapy for at least one year may pursue these options (13). However, many transgender men and women will seek hormone therapy without plans to undergo surgical intervention (14).

[1] Formerly referred to as cross-sex hormones or cross-hormone therapy

Those who pursue surgery may do so in various amounts, pursuing one or any combination of top, bottom, or other type of surgery that best aligns with their gender identity.

While enabling transgender individuals to achieve a desired physical appearance and alleviating gender dysphoria, gender-affirming interventions may also have deleterious effects on reproduction and fertility (15–17). These adverse effects on reproductive health have caused several groups, including WPATH, the Endocrine Society, the American Society for Reproductive Medicine, and the University of California San Francisco Center of Excellence for Transgender Health, to issue strong recommendations that transgender individuals be counseled on the various strategies available to preserve fertility prior to transition, and that these options be made readily available for those individuals wishing to utilize them (10,13,18,19).

Early access to fertility preservation (FP) is particularly pertinent for transgender adolescents, who are presenting for medical attention at higher rates than previously seen (6,11,20–24). Adolescents who undergo FP procedures before transition benefit from (1) preservation of fertility prior to the onset of the deleterious reproductive effects of GAH detailed above and (2) the avoidance of later interruption of their GAH therapy in order to undergo FP. Individuals who have transitioned and wish to become parents or undergo FP are advised to stop their GAH, which presents a challenge when cessation of GAH risks the return of unwanted sex characteristics and potential exacerbation of gender dysphoria (13). Therefore, healthcare providers—in addition to validating adolescents in their transgender identity through medical therapy—should ensure that adolescents make timely and fully-informed decisions about their future fertility prior to transition. Ideally

transgender adolescents and their families will take advantage of reproductive technologies when desired and appropriate and avoid potential future distress. However, no prior studies to our knowledge have prospectively examined the decision-making experiences of transgender adolescents surrounding FP and future parenthood.

Our study addresses this gap in the literature in several ways. First, the study examines transgender adolescents' baseline knowledge about reproductive health and fertility to establish their ability to participate in decision-making in these areas. Second, the study characterizes transgender adolescents' goals for future fertility and parenthood to determine their reproductive priorities. Third, the study measures the reproductive concerns of transgender adolescents to identify potential barriers to FP in this population. Finally, the study details perceived information gaps about reproductive health and fertility to identify areas for educational improvement.

1.2 Terminology

When referring to gender and sexuality, a wide range of terminology exists (13,19,25–28). Here we specify the terms and definitions used in this thesis. However, we recognize that these terms are continuously changing, and preferences for word choice may vary across individuals, cultures, settings, and time.

Birth-assigned sex —an individual's designation as male or female—is typically made at birth based on the phenotypic appearance of external genitalia or the physiological basis of karyotype or hormonal profiles. I*ntersex*, or more recently *disorders of sex development*, may be used for individuals born with anomalies of the sex chromosomes, gonads, reproductive tract, or genitalia (27,28). For these individuals, the dichotomous designation as male or female may not be clear.

Gender identity—an internal, inherent sense of being male, female, somewhere in between, both, or neither—may be consistent with or different from birth-assigned sex. *Cisgender* refers to individuals for whom gender identity is congruent with birth-assigned sex. *Transgender* is the umbrella term for those whose gender identity is incongruent with the identity typically associated with birth-assigned sex. For example, a transgender male identifies as male but is birth-assigned female. Likewise, a transgender female identifies as female but is birth-assigned male. Alternative terms for these identities are female-to-male (FtM) and male-to-female (MtF), respectively. *Gender non-conforming* individuals have a gender identity that differs from their birth-assigned sex but may be more fluid, complex, or less clearly defined than a transgender identity (19). For example, gender-nonconforming individuals may experience themselves as a male or female only part of the time, as both genders, as neither gender, or as a gender "other than" male or female (29). They may refer to themselves as transgender or as gender non-binary, gender queer, gender fluid, gender creative, or non-cisgender (30). This diversity of gender identities promotes the idea that gender identity exists on a spectrum or continuum rather than as a set of distinct and fixed identities (6).

Of note, sexual orientation is distinct from birth-assigned sex and gender identity. Sexual orientation signifies an individual's identity based on emotional, romantic, or sexual attraction to another person or group of people. Therefore, any combination of birth-assigned sex, gender identity, and sexual orientation may occur in a given individual.

When birth-assigned sex and gender identity differ, a pervasive and ongoing sense of distress known as *gender dysphoria* may result. It is important to note that not all

transgender and gender non-conforming individuals experience gender dysphoria. In addition, the terminology used to describe this distress has evolved over time. *Transsexual* has been a term historically used to describe individuals whose gender identity differed from birth-assigned sex (13,25). Transsexualism was first recognized as a diagnostic term in the *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition* (DSM-III) (31). However, critics have noted that the term *transsexual* fails to address the distress associated with cross-gender identification (32). Additionally, *transsexual* is a misnomer, as the incongruence is related to gender identity and not to sexuality (13). Therefore the term *transsexual* was replaced by *gender identity disorder* in the DSM-IV to denote impairment (32) and again by *gender dysphoria* in the DSM-V (Appendix A) to remove the stigma associated with the diagnosis (33). However, *transsexual* is still in use in some medical settings and by organizations such as the Endocrine Society and WPATH to refer to those individuals have begun or have completed the process of gender transition (10,13,26). For this thesis, we will forego the term *transsexual* and use the umbrella term *transgender* to include those with gender dysphoria who have or have not transitioned.

Transition or *gender affirmation* is the complex process of changing one's social or physical characteristics to better align with gender identity (8). Social transition may include modifying dress, behavior, or identifying names and pronouns to match gender identity. Physical transition, achieved through gender-affirming medical therapy or surgery, may enhance social transition by easing the shift to new styles of dress, social activities, or legal documentation that may not otherwise be possible (29). WPATH

guidelines specify that social transition occur prior to physical transition (13), but some individuals may pursue social transition alone.

1.3 Epidemiology

1.3.1 Prevalence of transgender identity in adults

Epidemiologic data on transgender individuals has been difficult to establish. Prior to 2007, United States census data and national surveys such as the National Health Interview Survey did not inquire about transgender identity (34). Most studies relied on self-presentation to a healthcare provider (35) or small statewide surveys (36,37). Prevalence estimates from these studies likely understate the true population of transgender individuals, given widespread social stigma and discrimination (5,29,38), misclassification of transgender identity as a sexual orientation rather than gender identity (39), and non-representative sampling.

More recent analyses of larger population-based studies have suggested that the prevalence of transgender adults in the United States is between 0.39% and 0.60%, or 1 to 1.4 million adults (1,34). A slight majority of transgender adults identify as MtF, with the remaining population identifying as either FtM or gender non-conforming (39,40).

1.3.2 Prevalence of transgender identity in children and adolescents

Children may present with gender non-conforming or cross-gender behavior in early toddlerhood as early as age two (41). Holt *et al.* studied the demographics of 218 children with gender dysphoria who presented for specialized care in the United Kingdom. Most gender dysphoric children recognized that their gender identity was different from their birth-assigned sex by age 6 and almost all by age 12 (42). Similarly, Olson *et al.* found

that the majority of 101 transgender youth realized their gender incongruence by eight years old (2). The average age of presentation is broad, ranging from 8.3 to 19 years old (2,42,43), and may reflect differences in access to gender-specific care and cultural acceptance. Since the early 2000s, the number of referrals to specialized pediatric gender clinics has drastically increased (11,21–24). It is possible that the increase in referral rates reflects a true increase in the prevalence of gender dysphoria; however, the rapidity of this increase in referral rates more likely indicates widening social acceptance and access to information on the part of patients (23,24) and expanded recognition and clinical interest in treating gender dysphoria on the part of providers (21,22).

Of the sparse epidemiological data available, the overall prevalence of transgender and gender non-conforming identity seems to decrease over the lifespan, with the highest rate in childhood and lowest rate in adulthood. A large study of 879 children from the general Dutch population reported a 5.8% prevalence of gender variant behavior, including behaving like the opposite sex or wishing to be of the opposite sex (44). The prevalence is even lower in adolescents than in children. Almeida *et al.* found that 1.4% of 1032 high-school students in Boston considered themselves to be transgender (45). Similarly, Clark *et al.* reported that 1.2% of 8166 high-school students in New Zealand identified as transgender. Interestingly, 2.5% of students were unsure about their gender (46).

This data suggests gender dysphoria or gender variant behavior in children will most often resolve by adolescence, obviating the need for transition. Reported rates of persistence of gender dysphoria from childhood to young adulthood have been low, ranging from 12 to 27% (43,47–49). Long-term follow-up of children with gender variant

behavior has suggested that this behavior in childhood is a stronger indicator of same-sex sexual orientation than of transgender identity (43,44,48).

Children whose feelings of gender dysphoria persist in adolescence are more likely to experience continued gender dysphoria and pursue transition. Few prospective studies are available, but de Vries and colleagues longitudinally followed a cohort of 70 gender dysphoric patients from adolescence into young adulthood. The cohort was assessed in early adolescence at the start of puberty suppression medication, in middle adolescence at the start of GAH, and, for a subset of 55 patients, in young adulthood one year after gender reassignment surgery (50,51). Only one patient in the cohort of 70 dropped out of care, and two refused continued participation, suggesting an almost complete rate of persistence of gender dysphoria from adolescence to adulthood.

1.4 Reproductive Goals and Parenthood Desires

Many transgender adults are currently parents, and those who are not have high rates of desiring parenthood. To determine the prevalence of parenthood in transgender adults, Stotzer *et al.* conducted a systematic review of 51 studies examining transgender parenthood. Results from the review indicated that between 25% and 46% of transgender adults report being parents (52). For comparison, about 65% of adult males and 74% of adult females in the general U.S. population report being biological parents (53). The systematic review did not distinguish between biological and non-biological parenthood, yet a considerable number of transgender adults favor biological parenthood. A 2017 U.S. survey found that 50% of 32 transgender adults without children desired biological children in the future (54). A cohort of MtF adults in Belgium reported similar results,

with 50% of 121 participants disclosing a preference for biologically-related offspring (55).

In contrast to the parenthood goals of transgender adults, the parenthood goals of transgender adolescents have been less well described in the literature. Abstracts from unpublished studies have provided some insight and have suggested that the goals were not necessarily biological parenthood. Clark *et al.* prospectively surveyed 25 transgender adolescents and found that over half strongly desire some form of future parenthood (biological or non-biological) (56). Chen *et al.* surveyed a larger sample of 172 transgender adolescents online and found that adolescents were almost two times more interested in adoption than in biological parenthood (71% vs. 38%) (57). Notably, these results were preliminary, and final results have yet to be published.

The preference of transgender adolescents for non-biological over biological parenthood is not surprising. Unlike transgender adults who may have already transitioned or may already have children, transgender adolescents focused on transitioning may have never considered their attitudes and beliefs about parenthood; thus, the idea of having a biological child may be both physically and psychologically difficult for an adolescent in this situation. Moreover, transgender individuals are encouraged to stop GAH during attempts to conceive and during pregnancy (10,13). Stopping GAH may be unappealing because of the development of unwanted secondary sexual characteristics and worsening of gender dysphoria. Lastly, the process of sexual intercourse and the feminizing experience of pregnancy are, for many, in conflict with their gender identity and pose significant barriers to biological parenthood (54).

1.4.1 Routes to Biological Parenthood

Transgender adolescents should be informed about the possible effects of GAH on fertility and, for those interested in future biological parenthood, about the options available for FP and future reproduction. Banking or freezing (also known as cryopreservation) of mature oocytes and sperm are the most established and reliable methods of FP. Testicular sperm extraction (TESE) followed by sperm banking is additional option that has been successfully performed in MtFs at the time of gender-affirming surgery (58). However, these methods require attainment of puberty for optimal results (59). For adolescents who have not completed puberty, ovarian tissue cryopreservation (OTC) and testicular tissue cryopreservation are potential routes of preserving fertility potential but are still considered experimental in pre- and peri-pubertal adolescents with immature gametes (60,61). To date, over 60 live births from OTC have been reported in cisgender adults after autologous re-implantation of banked mature tissue (62,63). However, re-implantation of ovarian tissue may be undesirable for FtMs because of the restoration of ovarian activity and resultant increased exposure to estrogen. A strategy to avoid ovarian tissue re-implantation would involve the collection of oocytes from ovarian tissue, development of the oocytes to maturity *in vitro* (a process known as *in-vitro* maturation or IVM), and freezing of the mature oocytes. This strategy is still in its infancy with few reported cases of success (64,65) and is unlikely to be a feasible option for most FtMs currently wishing to preserve fertility.

After transition, stored gametes can be used in conjunction with assisted reproductive technologies (ART) or other fertility services to attempt pregnancy. The main form of ART is in vitro fertilization (IVF), in which a retrieved oocyte and sperm

are passively combined in a laboratory and the resulting embryo transferred into the uterus. IVF may be augmented by intracytoplasmic sperm injection (ICSI), in which the retrieved oocyte is injected directly with a sperm and the resulting embryo transferred into the uterus. Other assisted fertility options include intrauterine insemination (IUI), in which sperm are introduced into the uterus to facilitate fertilization, and third-party assisted fertility, such as gamete donation or surrogacy. Light *et al.* surveyed 41 FtMs who experienced pregnancy after transition and found that 20% used ART or other fertility services to conceive (66). Similarly, case reports of transgender individuals who underwent gamete banking before the start of GAH include descriptions of successful pregnancies and live births after unfreezing and ICSI (67,68).

Transgender individuals on GAH who choose not to undergo FP procedures may still experience spontaneous conception. One-fifth of the 41 previously pregnant FtMs in the Light study conceived while still amenorrheic (with cessation of menses, in these cases after testosterone use), and one-fourth had unplanned pregnancies while taking testosterone (66). Thus, testosterone use does not necessarily preclude ovulation and pregnancy and should not be considered a contraceptive.

Indeed, the role of testosterone on fertility in FtMs remains unclear. When studying fertility in birth-assigned females, one way to determine ovarian reserve, or the remaining supply of oocytes, is by counting the number and type of follicles in each ovary. A follicle is the functional anatomical structure within the ovary that contains an oocyte as it matures over an ovarian cycle. Several studies have demonstrated normal numbers of early follicles in the ovaries of FtMs compared to published cisgender controls after more than a year of testosterone therapy, suggesting that GAH has a

minimal effect on ovarian reserve (69,70). On the other hand, other studies have found that the ovaries of FtMs on long-term testosterone have significantly higher numbers of atretic follicles than the ovaries of cisgender controls (71,72). Atretic follicles are those that have undergone degeneration and are no longer available for maturation, ovulation, and potential fertilization. This process normally occurs with each ovarian cycle but, if occurring at an accelerated rate as above, can indicate an increased risk for premature ovarian failure and diminished fertility. Because birth-assigned females are unable to generate new follicles, this decrease in ovarian reserve is irreversible.

For MtFs, estrogen has been shown to be associated with impaired fertility. Histological studies have shown decreased spermatogenesis—sperm formation and maturation—and sperm motility after long-term estrogen therapy (73–75), suggesting that GAH decreases the both the number and quality of mature sperm available for fertilization. However, the suppressive effect of estrogen on sperm appears to be reversible based on available studies, with semen parameters returning to normal within three months of GAH cessation (73).

1.4.2 Fertility Preservation Utilization

With the advent of new technologies to achieve biological parenthood, an increasing number of patients are opting for FP consultation (68,76), while utilization rates continue to remain low. Only 3 to 4% of MtF adolescents seen at two specialized gender clinics actually completed sperm cryopreservation (77,78). Jones *et al.* reported that nine of eleven MtF adults at a single clinic referred for FP consultation opted for sperm cryopreservation, although the total number of MtFs who were seen but declined FP consultation was not clear (68). In a survey-based study of 121 MtF adults who had

not previously undergone FP, participants reported that their low desire to have sperm cryopreserved was due to distress about masturbation to procure a semen sample and concern that storage of sperm would inextricably link them to their male identity (55).

In general, the literature suggests an even lower interest in FP for FtM than for MtF patients. Only 37.5% of 50 FtM adults surveyed in Belgium would have preserved oocytes during transition, but the technique was not available at the time (79). None of three FtM adults in the Jones study chose to undergo oocyte cryopreservation. Similarly, none of 23 FtM adolescents at one clinic (77) and only one of six FtM adolescents at a 105 patient clinic (78) who received fertility counseling elected to undergo oocyte cryopreservation. Reasons cited included financial restraint, invasiveness of the oocyte retrieval procedure itself, and unwillingness to temporarily stop androgen therapy in order to undergo ovarian stimulation (68,78). The findings above suggest that for both FtMs and MtFs, FP procedures may be declined largely because they provoke feelings of gender dysphoria. However, in adolescents the reasons for FP refusal were obtained retrospectively from the few patients who received formal FP counseling; no prospective data are available regarding how the general transgender adolescent population presenting for care prioritizes their fertility potential and reproductive health.

1.5 Current Study

Transgender individuals pursuing transition in adolescence must decide how to reconcile this transition with the potential for infertility. Understanding how this reconciliation occurs has important clinical implications for the counseling and treatment of adolescents with gender dysphoria. Existing literature has focused primarily on patients diagnosed with cancer facing gonadotoxic therapies. Adolescents with recent cancer diagnoses and

their families rank fertility as a high priority, second only to the achievement of good health (80,81), and adult survivors of childhood cancer express regret about missed opportunities for FP (82,83). The same reproductive and fertility priorities have not yet been established in transgender adolescents.

Thus, the present study addresses this gap in knowledge by exploring the baseline knowledge and attitudes about reproductive health and fertility in transgender youth who attend an academic, university-affiliated adolescent gender clinic. A secondary aim is to determine which sociodemographic and gender transition factors may affect these outcomes. The hypothesis of this study is that most transgender adolescents will desire future parenthood but will have low baseline knowledge about transgender fertility topics, leading to substantial levels of concern about future reproduction and greater perceived information needs. To test this hypothesis, a cross-sectional survey was administered over a one-year period to transgender youth at a single university-affiliated clinic (the Yale Pediatric Gender Program, or YGP). By comparing survey responses to demographic and medical data, the study also investigated differences in responses according to different ages and stages of the transition process.

2 Methods

This survey is a single-center, cross-sectional study designed to evaluate the fertility-related experiences of transgender adolescents. The prospective survey was made available in a clinical setting during patient appointments at the YGP, a university-affiliated interdisciplinary clinic with healthcare professionals specializing in child psychiatry and pediatric endocrinology and consultants in gynecology and plastic surgery. The Human Investigations Committee at Yale University approved this study.

We obtained written consent from all adults and written assent and consent from all minors and their parents who agreed to participate prior to survey completion.

2.1 Participants and Recruitment

Patients were included for study participation if they met the following criteria: (i) self-identified as transgender or gender non-conforming, (ii) age 12 to 22 years, and (iii) presented for gender-affirming medical treatment at the YGP between October 2016 and August 2017. The lower age limit of 12 (or grade 6) was the age at which the majority of Connecticut schools reported teaching students about sexual education topics (84). Patients were excluded from study participation if they identified as cisgender, were not between the ages of 12 and 22, or did not respond to the questions being explored.

The research team identified potential participants from a convenience sample of patients attending clinic for routine visits. Patients who met inclusion criteria were approached by a member of the research team who was not involved in the patient's clinical care and asked to participate. All patients who agreed to participate signed a consent form and completed the survey once, either during their clinic appointment or during a separate mental health appointment determining readiness for transition. The current standard of care at the YGP consists of the completion of a number of standardized questionnaires as well as an individualized interview with a mental health professional prior to receiving gender-affirming medical treatment. Thus completing the survey concurrently with other questionnaires at a clinic or mental health appointment did not detract from patient care.

2.2 Data Collection

2.2.1 Outcome Measures

General socio-demographic and medical data were obtained from participants' electronic medical record. To assess the fertility-related experiences of adolescents who face potential infertility as a result of medical treatments, participants completed a prospective survey developed by an interdisciplinary research team. Potential items for the survey instrument were adapted from previously published questionnaires validated in the young adult oncology population for assessment of fertility desires, concerns, and goals (85–88) and were designed to examine factors in four domains: baseline knowledge, attitudes toward future parenthood, reproductive concerns, and unmet information needs.

Baseline Knowledge: To establish information on participants' baseline knowledge of survey topics, participants answered five true/false/unsure items derived from the 'Preserving Reproductive Opportunity After Cancer Treatment' (PROACT) survey (86). The PROACT survey consists of a validated knowledge index evaluating comprehension of fertility preservation topics in female oncology patients following consultation with an infertility specialist but prior to gonadotoxic medical treatment. Topics in our survey included basic comprehension of general reproduction, infertility in the general population, the role of physicians in predicting infertility, and the basic concept of fertility preservation. An additional question regarding the effects of GAH on fertility was added by the research team. Mean total knowledge scores were calculated, with one point awarded for each correct response and no points awarded for incorrect or unsure responses. Overall each participant received an averaged score between 0 and 5. Participants were also asked an investigator-designed question about sources used for

information on fertility preservation prior to survey completion and were allowed to indicate as many sources as applicable.

Attitudes toward Future Parenthood: To assess the reproductive desires in our patient population, participants were asked two investigator-designed questions. The first asked whether future parenthood was important to them (yes, no, or unsure). They were also asked to indicate their preferred forms of future parenthood including biological parenthood or alternative parenthood such as adoption or fostering.

Reproductive Concerns: To determine participant concerns about fertility and parenthood, seven items were adapted from the Reproductive Concerns after Cancer (RCAC) Scale (87,88). This scale measured reproductive concerns in young adult cancer survivors across six subscales: fertility potential, partner disclosure, child's health, acceptance, becoming a parent, and personal health. The personal health category in our population was modified to include concerns regarding a possible delay in initiation of GAH. Participants were asked if they worried about their ability to have a child someday (fertility potential), if they worried about telling their potential partner that they may not be able to have a child (partner disclosure), if they wondered whether their future child would have a high chance of being transgender (child's health), if they accepted the inability to have a child someday (acceptance), if they worried that trying to have a child would take too much time and effort and if they felt stressed when thinking about trying to have a child (becoming a parent), and if they felt concerned about delaying transition one month or more in order to preserve eggs or sperm (delaying transition).

Responses were rated on a 5-point Likert scale where 1= "strongly disagree" and 5= "strongly agree." Mean overall and subscale scores were calculated. Higher mean

scores suggested greater reproductive concerns, with mean scores of 0-1.00 indicating low concern, 1.01-2.00 slight concern, 2.01-3.00 fair concern, 3.01-4.00 moderate concern, and 4.01-4.99 significant concern.

Unmet Information Needs: To determine perceived information needs in this population, we adapted five survey items from Benedict *et al.* (88), which assessed unmet information needs and decisional conflict surrounding fertility preservation in young adult cancer survivors following chemotherapy. Participants in our survey indicated (yes/no) whether they had as much information as they wanted regarding the risk of infertility with GAH, sources of fertility assessment, options for fertility preservation, risks and benefits of delaying GAH for fertility preservation, and options for alternative family-building. Responses were scored by summing item responses (yes = 0 and 1 = no), with total scores ranging from 0-5. Higher total scores suggested greater perceived information needs. Additional investigator-initiated questions asked participants about preferred resources for receiving additional information.

2.2.2 Validity

The survey instrument was assessed for validity, clarity, and ease of application. Content experts in pediatric and adolescent gynecology (J.C.)[2], reproductive endocrinology and infertility (A.K.), and pediatric endocrinology (S.W., S.B., A.P.) reviewed survey questions for content validity and item clarity. A non-physician epidemiologist (L.L.) with minimal transgender experience further assessed the survey for face validity and item clarity. Finally, a child psychiatrist (C.O.) specializing in transgender adolescent

[2] J.C. = Julia Cron, MD; A.K. = Amanda Kallen, MD; S.W. = Stuart Weinzimer, MD; S.B. = Susan Boulware, MD; A.P. = Anisha Patel, DO; L.L. = Lisbet Lundsberg, PhD; C.O = Christy Olezeski, PhD

care adjusted the language of the survey instructions and questions to a level appropriate to the patient population and provided feedback about the feasibility of survey administration in the clinic setting. Minor modifications were made according to the reviewers' recommendations. These recommendations included adding an "unsure" category, changing the specialized term "cross-hormone therapy" (now referred to as gender-affirming hormones or GAH) to the patient-friendly term "hormones," changing "male" and "female" to the trans-friendly terms "a person born male" and "a person born female," and removing scale numbering to prevent undue influence of scoring on participant responses. The final survey consisted of 22 questions across four domains detailed above. We did not complete pilot testing with transgender youth prior to survey administration because of anticipated small sample size of eligible participants.

2.3 Statistical Analysis

All statistical analyses were performed using GraphPad Prism version 7.0c (GraphPad Software, La Jolla California, www.graphpad.com). Descriptive statistics were used to summarize participants' baseline characteristics. Frequency and percentage were used for categorical data and mean and standard deviation for continuous data.

Unpaired *t*-tests and one-way analyses of variance were conducted to assess differences in continuous data, including mean scores in baseline knowledge, reproductive concern, and unmet information needs. Fisher's exact test was used to determine differences in categorical data, including frequency of demographic data and attitudes toward future parenthood. Outcomes were compared across the sociodemographic variables of birth-assigned sex, race, insurance status, and age. The age groups of 12 to 14, 15 to 17, and 18 to 22 years were selected to represent early,

middle, and late adolescence (89). Additional variables included use of puberty blockers or GAH. A P value < 0.05 was considered statistically significant for all analyses.

2.4 Research Team Contributions

The author (A.A.) was responsible for the study design and implementation; data collection and analysis; and drafting of the thesis work. J.C., A.K., and C.O. contributed to the study design through critical review of the survey questionnaire, and J.C. and A.K. critically reviewed the thesis work for accuracy and intellectual integrity.

3 Results

3.1 Participant Characteristics

Of the 38 eligible patients seen in clinic during the study time period, a total of 23 transgender adolescents completed the survey (61% participation rate). Seven additional patients were ineligible for survey completion due to age less than 12. There were no significant differences in socio-demographic data between eligible participants and non-participants during the study period (all p>0.05, Appendix B). Most participants completed the survey at a routine follow-up visit with a median interval between initial presentation and survey completion of 5.6 (IQR: 1.2-10.4) months.

Overall, the mean age of participants was 16.2 ± 2.5 years at the time of survey completion (Table 1). Most participants were birth-assigned females (n=17/23, 74%). Among those who were birth-assigned females, the majority (n=15/17, 88%) identified as FtM with a few (n=2/17, 12%) identifying as gender non-conforming. The remaining participants were birth-assigned males who identified as MtF (n=6/23, 26%). Of the 23 participants, ten (43%) were on a GnRHa for puberty blockade and eight (35%) were on

GAH at the time of survey completion. Of the participants on GAH, most (n=7/8, 88%) were receiving testosterone, and one (n=1/8, 13%) was receiving estrogen. Five participants (n=5/23, 22%) were not on any form of medical therapy at the time of survey completion. No significant differences existed between birth-assigned females and birth-assigned males in regard to age, race or ethnicity, insurance status, and use of puberty blockers or GAH (all p>0.05, Table 1).

Table 1. Participant characteristics by birth-assigned sex.
Sociodemographic and medical data were extracted from patient medical records and compared between birth-assigned females and males using the unpaired *t*-test for continuous variables and Fisher's exact test for categorical variables.

Participant Characteristic	Total (N=23)	Birth-Assigned Sex		P value
		Female (N=17)	Male (N=6)	
Age (years), Mean ± SD				
Initial Presentation	16.0 ± 2.6	16.0 ± 2.2	15.0 ± 3.8	0.44
Survey Completion	16.2 ± 2.5	16.0 ± 2.3	16.2 ± 3.2	0.87
Race/Ethnicity, n(%)				1.00[A]
White/Caucasian	18 (78)	13 (76)	5 (83)	
Black/African-American	2 (9)	2 (12)	0 (0)	
Hispanic or Latino	2 (9)	1 (6)	1 (17)	
Asian	1 (4)	1 (6)	0 (0)	
Insurance, n(%)				1.00
Public	8 (35)	6 (35)	2 (33)	
Private	15 (65)	11 (65)	4 (66)	
Use of Puberty Blockers or GAH, n(%)				0.58
Yes	18 (78)	14 (82)	4 (66)	
No	5 (22)	3 (18)	2 (33)	

GAH = gender-affirming hormones (testosterone or estrogen)
[A] Caucasian vs. Non-Caucasian

3.2 Baseline Knowledge

Participants answered a series of five questions assessing their baseline knowledge about reproductive health and fertility topics (Table 2), with a mean total knowledge score of 3.78 ± 0.80 out of 5 possible points (Table 3). Most adolescents had basic knowledge about infertility (Q1) and fertility preservation (Q5) and correctly understood that GAH may affect fertility (Q2). However, only a slight majority of participants correctly

understood how fertilization occurs (Q4), and fewer than half of participants understood the limitations of physicians in predicting the effects of GAH on fertility (Q3).

Table 2. Baseline knowledge questions about reproductive health and fertility
Participants were asked a series of five true/false/unsure questions to establish baseline knowledge about reproductive health and fertility. % correct indicates the percentage of the 23 total participants who answered each question correctly.

Question	Correct Answer	% Correct
Q1. All people who want to become birth parents are able to	False	91
Q2. Hormones may affect a person's ability to have a child in the future	True	96
Q3. A doctor can accurately predict the effect that hormones will have on a person's ability to have a child in the future	False	44
Q4. An egg from a person born female and a sperm from a person born male are needed to make a baby	True	61
Q5. Storing eggs or sperm is one way to preserve the ability to have a child in the future	True	87

Over half of participants (n=16/23, 70%) had discussed the impact of GAH on fertility and options for FP with someone prior to survey completion. The most common source of information was a physician (n=15/23, 65%; Figure 1). The next most common sources of information were friends and family (n=12/23, 52%) and online resources (n=9/23, 39%). Almost 1/3 of participants (n=7/23, 30%) reported never receiving information about fertility topics from any source. Five of these seven participants (71%) were either new patients or follow-up patients not receiving gender-affirming medical therapy, but two (29%) were follow-up patients on a GnRHa or testosterone at the time of survey completion.

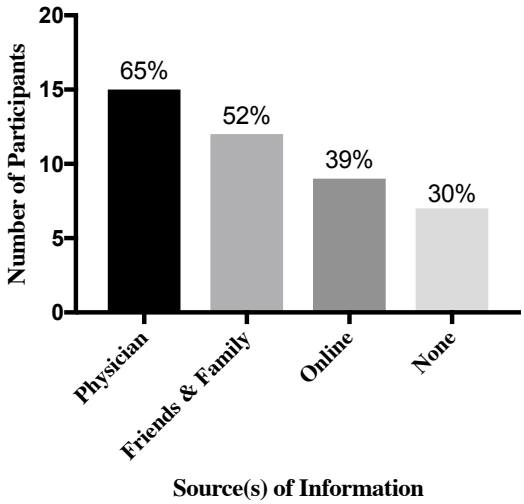

Figure 1. Previous source(s) of information about gender-affirming hormone therapy and fertility Participants specified how they previously received information. Percentage over bar indicates the proportion of total sample size who had received information from an indicated source. Participants were given the option to select as many sources as applicable, so total percentage exceeds 100%.

We analyzed the difference between knowledge scores among sub-groups to determine potential predictors of the knowledge score (Table 3). Participants who had discussed GAH and fertility topics with someone prior to survey completion had significantly higher scores than those who had no previous discussion ($p<0.05$). Additionally, race approached significance, with Caucasian participants performing better than those who were not Caucasian ($p=0.06$). Other socio-demographic factors, use of puberty blockers or GAH, and time between initial presentation and survey completion had no notable effect on knowledge scores (all $p>0.05$).

Table 3. Mean baseline knowledge score by sociodemographic and gender transition variables. Mean total knowledge scores were calculated with a maximum total score of 5. Differences in mean total knowledge scores were compared by sociodemographic and gender transition variables using analyses of variance. N(%) indicates the number and percentage of participants in each participant group. Bolded numbers highlight significant differences in mean knowledge score within a participant group.

Participant Group	N(%)	Knowledge Score, Mean (SD)[A]	P value
Total Sample	23 (100)	3.78 (0.80)	-
Sociodemographics			
Birth-Assigned Sex			
Female	17(74)	3.71 (0.85)	0.46
Male	6 (27)	4.00 (0.63)	
Age (years)			
12 to 14	6 (26)	3.83 (1.17)	
15 to 17	12 (52)	3.83 (0.72)	0.86
18 to 22	5 (22)	3.60 (0.55)	
Race			
Caucasian	18 (78)	3.20 (0.45)	0.06
Non-Caucasian	5 (22)	3.94 (0.80)	
Insurance			
Public	8 (35)	3.87 (0.83)	0.50
Private	15 (65)	3.63 (0.74)	
Transition Process			
Previous discussion about fertility topics			
Yes	16 (70)	4.00 (0.73)	**0.04**
No	7 (30)	3.29 (0.76)	
Time between initial presentation and survey completion			
≤ 6 months	12 (52)	3.58 (0.81)	0.22
> 6 months	11 (48)	4.00 (0.77)	
Use of Puberty Blockers or GAH			
Yes	18 (78)	3.78 (0.81)	0.96
No	5 (22)	3.80 (0.84)	

GAH = gender-affirming hormones (testosterone or estrogen)
[A] Maximum score of 5

3.3 Attitudes toward Future Parenthood

Overall, participants were about equally divided in reporting future parenthood was important (n=7/23, 30%), not important (n=9/23, 39%), or undecided (n=7/23, 30%). The likelihood of viewing future parenthood as important did not differ significantly across sociodemographic or gender transition variables (Table 4, all p>0.05).

When asked which type of parenthood they would prefer, participants indicated adoption more frequently than all other forms of parenthood (n=16/23, 70%). Birth-assigned females were significantly more likely to prefer adoption than birth-assigned males ($p<0.05$). After adoption, the most commonly reported preferences for parenthood were fostering (n=10/23, 43%), having one's own biological child (n=5/23, 22%), and having a partner's biological child (n=5/23, 22%). Although surrogacy was endorsed by the fewest numbers of participants (n=4/17, 17%), those who preferred surrogacy were significantly more likely to be birth-assigned male than birth-assigned female ($p<0.05$). Preferences for type of parenthood did not vary significantly by other socio-demographic or gender transition variables (Appendix C, all $p>0.05$).

3.4 Reproductive Concerns

Participants as a whole had a fair level of reproductive concern with a mean total score of 2.16 ± 0.51 out of a possible 5 points (Table 5). The greatest reproductive concerns were related to the postponement of transition and to the process of becoming a parent. For example, more than one-third of participants were concerned about delaying their transition to undergo fertility preservation (n=8/23, 35%). More than half of participants (n =12/23, 52%) reported feeling stressed when thinking about trying to have a child someday, and almost one third were concerned about the time and effort involved in trying to have a child (n=7/23, 30%).

The level of concern about the process of becoming a parent differed significantly according to desire for parenthood and age. Interestingly, those who did not consider future parenthood to be important had the highest level of concern about the process of becoming a parent ($p<0.0001$, Appendix D) and the lowest levels of concern about their

fertility potential ($p<0.01$) and about disclosing potential infertility to their partner (p $p<0.05$). Participants in early adolescence (age 12 to 14) had a significantly higher level of concern about becoming a parent than those in middle (age 15 to 17) or late (age 18 to 22) adolescence ($p<0.0001$).

Participants expressed acceptance of possible infertility and had low levels of concern about having a child who might be transgender. Level of reproductive concern did not differ significantly by birth-assigned sex or by use of puberty blockers or GAH (all $p>0.05$, Appendix D).

Table 4. Attitudes toward future parenthood.
Participants indicated the importance of future parenthood (important/not important) and their interest (yes/no) in different forms of biological or non-biological forms of parenthood. All values are n(%), or the number and percentage of participants who responded important or yes to each category. A value of 0 means that no participant in a given group indicated importance or interest in that category. Differences in frequency of responses were compared by sociodemographic and gender transition variables using Fisher's exact test. P-values are listed in Appendix C. Bolded numbers highlight significantly different frequencies of importance/interest within a participant group.

Participant Group	Future Parenthood Important	Biological Parenthood[A]			Alternative Parenthood[A]	
		Self Bio Child	Partner Bio Child	Surrogacy	Adoption	Fostering
Total Sample	7 (30)	5 (22)	5 (22)	4 (17)	16 (70)	10 (43)
Sociodemographics						
Birth-Assigned Sex						
Female (N=17)	5 (29)	3 (18)	4 (24)	**1 (6)***	**14 (82)***	9 (53)
Male (N=6)	2 (33)	2 (33)	1 (17)	**3 (50)**	**2 (33)**	1 (17)
Age (years)						
12 to 14 (N=6)	1 (17)	2 (33)	1 (17)	2 (33)	5 (83)	3 (50)
15 to 17 (N=12)	6 (50)	2 (17)	2 (17)	1 (8)	7 (58)	4 (33)
18 to 22 (N=5)	0 (0)	2 (20)	2 (20)	1 (20)	4 (80)	3 (60)
Race						
Caucasian (N=18)	6 (33)	3 (17)	4 (22)	2 (11)	13 (72)	8 (44)
Non-Caucasian (N=5)	1 (20)	2 (40)	1 (20)	2 (40)	3 (60)	2 (40)
Insurance						
Public	3 (38)	3 (38)	2 (25)	3 (38)	6 (75)	4 (50)
Private	4 (27)	2 (13)	3 (20)	1 (7)	10 (67)	6 (40)
Transition Process						
Use of Puberty Blockers or GAH						
Yes (N=18)	6 (33)	3 (17)	5 (28)	3 (17)	14 (78)	9 (50)
No (N=5)	1 (20)	2 (40)	0 (0)	1 (20)	2 (40)	1 (20)

GAH = gender-affirming hormones (testosterone or estrogen)
[A] Participants were given the option to select more than one; totals may exceed 100%
* $p<0.05$

Table 5. Reproductive concerns by participant characteristics.
Participants ranked how concerned they were about six areas of future reproduction. Answers were scored on a scale from 1 to 5, with 5 indicating the highest level of concern. Mean total score was calculated by averaging the scores across all six subscales for each participant. Differences in scores were compared using analyses of variance. P values are listed in Appendix D. Mean (SD) are mean scores with standard deviation in parentheses. Bolded numbers highlight significantly different levels of concern by analyses of variance within a participant group.

Participant Group	Subscale Scores, Mean (SD)						Total Score, Mean (SD)
	Fertility Potential	Partner Disclosure	Child's Health	Acceptance	Becoming a Parent	Delaying Transition	
Total Sample	1.82 (1.10)	2.04 (1.22)	1.61 (0.94)	1.57 (1.04)	2.61 (1.31)	2.57 (1.65)	2.16 (0.51)
Parenthood Desires							
Parenthood Important							
Yes	**2.50 (1.05)****	**3.17 (1.33)***	1.83 (0.75)	1.50 (0.84)	**2.25 (0.07)******	1.50 (1.22)	2.14 (0.57)
No	**1.00 (0)**	**1.56 (1.01)**	1.56 (0.88)	1.00 (0)	**3.61 (0.12)**	2.56 (1.67)	2.13 (0.44)
Unsure	**2.50 (1.22)**	**1.86 (0.90)**	1.71 (1.11)	1.86 (0.90)	**2.79 (0.27)**	3.14 (1.57)	2.45 (0.62)
Demographics							
Birth-Assigned Sex							
Female	1.88 (1.05)	2.12 (1.22)	1.82 (0.95)	1.41 (0.71)	2.79 (0.22)	2.41 (1.66)	2.18 (0.57)
Male	1.60 (1.34)	1.83 (1.33)	1.00 (0.63)	2.00 (1.67)	3.00 (0.20)	3.00 (1.67)	2.21 (0.55)
Age							
12-14	1.83 (1.33)	1.83 (0.93)	1.67 (1.51)	2.00 (1.67)	**3.33 (0.11)******	2.83 (1.60)	2.40 (0.66)
15-17	1.82 (1.08)	2.42 (1.44)	1.50 (0.67)	1.42 (0.79)	**2.46 (0.24)**	2.17 (1.75)	2.04 (0.56)
18-22	1.80 (1.10)	1.40 (0.55)	1.80 (0.84)	1.40 (0.55)	**3.20 (0.57)**	3.20 (1.48)	2.29 (0.36)
Transition Process							
Use of Puberty Blockers or GAH							
Yes	1.83 (1.04)	2.17 (1.20)	1.72 (1.02)	1.61 (1.09)	2.83 (0.14)	2.44 (1.62)	2.21 (0.58)
No	1.75 (1.50)	1.60 (1.34)	1.20 (0.45)	1.40 (0.89)	2.90 (0.48)	3.00 (1.87)	2.11 (0.51)

GAH = gender-affirming hormones (testosterone or estrogen)
* $p<0.05$
** $p < 0.01$
**** $p<0.001$

3.5 Unmet Information Needs

Out of 23 participants, 10 (44%) expressed a desire for more information about fertility topics. Of these 10, five (50%) had previously discussed fertility topics with a physician. The most common topics requested were options for fertility preservation (n=7/23, 30%) and the risks and benefits of delaying GAH to undergo fertility preservation (n=6/23, 26%; Figure 2). A minority of patients reported wanting more information about the possible effects of GAH on fertility (n=4/23, 17%). All participants (n=23/23, 100%) reported feeling satisfied with the amount of information they had about alternative family-building options such as adoption, fostering, or egg/sperm donation. Perceived information needs did not differ significantly by socio-demographic, transition process, parenthood desire, or reproductive concern variables (Table 6).

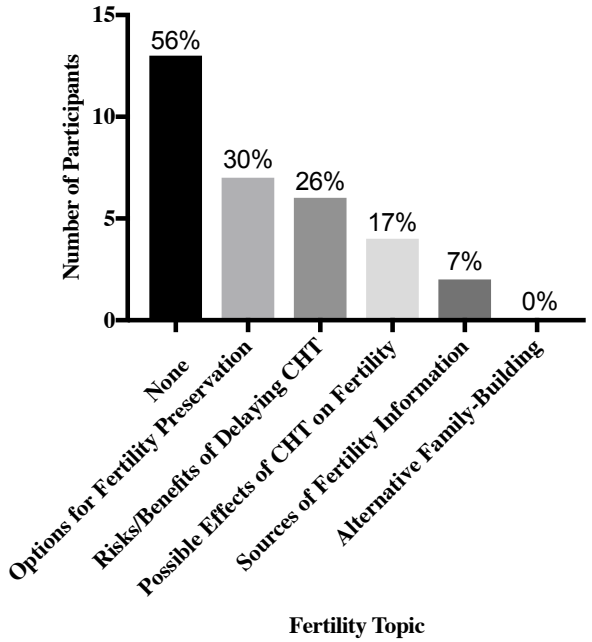

Figure 2. Perceived information needs about fertility topics.
Participants indicated fertility topics about which they would like more information. Percentage over bar indicates the proportion of total sample size expressing an information need about the fertility topic shown. Participants were given the option to select as many topics as applicable, so total percentage exceeds 100%.

Table 6. Unmet information needs by participant characteristics.
Participants were asked whether they had as much information as they would like on five fertility topics. Mean total scores were calculated with a maximum total score of 5 for each participant. Differences in mean total scores were calculated between variables within participant groups using analyses of variance. N(%) indicates the total number and percentage of participants in each participant group.

Participant Group	N(%)	Total Unmet Information Score, Mean (SD)	P value
Total Sample	23 (100)	0.83 (1.23)	-
Sociodemographics			
Birth-Assigned Sex			
Female	17 (74)	0.94 (1.39)	0.46
Male	6 (27)	0.50 (0.55)	
Age (years)			
12 to 14	6 (26)	1.33 (1.37)	
15 to 17	12 (52)	0.42 (0.90)	0.25
18 to 22	5 (22)	1.20 (1.64)	
Race			
Caucasian	18 (78)	0.94 (1.35)	0.39
Non-Caucasian	5 (22)	0.40 (0.55)	
Insurance			
Public	8 (35)	0.63 (1.06)	0.58
Private	15 (65)	0.93 (1.34)	
Transition Process			
Previous discussion about fertility topics			
Yes	16 (70)	0.69 (1.01)	0.43
No	7 (30)	1.14 (1.68)	
Time between initial presentation and survey completion			
≤ 6 months	12 (52)	0.50 (0.90)	0.19
> 6 months	11 (48)	1.18 (1.47)	
Use of Puberty Blockers or GAH			
Yes	18 (78)	0.94 (1.35)	0.39
No	5 (22)	0.40 (0.55)	
Parenthood Desires			
Parenthood Important			
Yes	7 (30)	0.57 (1.14)	
No	9 (39)	0.67 (1.00)	0.51
Unsure	7 (30)	1.27 (1.60)	
Reproductive Concern			
Level of Concern by Mean Score			
Low (0-2)	8	0.38 (0.52)	
Slight Concern (2-3)	13	0.92 (1.44)	0.23
Somewhat Concerned (>3)	2	2.00 (1.41)	

GAH = gender-affirming hormones (testosterone or estrogen)

4 Discussion

The primary goal of the study was to determine the knowledge and attitudes of transgender adolescents at a single center regarding fertility and future parenthood. The key findings of the study were as follows: (1) transgender adolescents possess basic knowledge about general reproductive health and fertility topics, yet almost half of participants incorrectly answered questions about the details of fertilization and the ability of physicians to predict the effect of GAH on fertility; (2) only one-third of transgender adolescents in our study considered future parenthood to be important. Interest in non-biological parenthood (adoption and fostering) was reported more than three times as frequently than interest in biological parenthood, particularly among birth-assigned females; (3) transgender adolescents overall had a fair level of concern about future reproduction, most commonly about the postponement of transition to undergo fertility preservation procedures and the time, stress, and effort of becoming a parent. Significant predictors of higher levels of reproductive concern included early adolescence and reporting future parenthood as unimportant; and (4) fewer than half of transgender adolescents requested additional fertility-related information, but those who did most commonly requested information about the risks and benefits of various fertility preservation options.

4.1 Baseline Knowledge

Contrary to our *a priori* hypothesis, we found that transgender adolescents in our clinic possess a basic understanding of general and transgender-specific reproductive health and fertility topics, as measured by correct responses to survey questions. These findings suggest that transgender adolescents understand general fertility topics and are able to

participate in making informed decisions about their reproductive health. Researchers have demonstrated the opposite in oncology patients, who also face potential infertility as the result of their medical therapy. Oncology patients often demonstrate poor reproductive health knowledge before (90) and after (91,92) cancer treatment. This lack of knowledge has led to poor patient satisfaction (93,94) and anxiety surrounding fertility (95). The difference in knowledge outcomes between our study and the oncofertility literature is likely due to differences in previous exposure to fertility-related information. Many oncology patients recall limited to no previous information about fertility topics (85,95), possibly because they are saturated with the amount of new information and the stress of a new cancer diagnosis (94,96). Depending on the stage and type of cancer, many oncology patients also may not have the time to process threats to their fertility or to undergo FP prior to medical treatment. In contrast, the majority (70%) of transgender adolescents in our study report receiving previous information about fertility topics, which, consistent with the findings of Balthazar *et al.* (90), was associated with significantly higher knowledge scores. Transgender adolescents in general have more time than oncology patients do to learn about the effects of treatment on their fertility and to make decisions about FP, if desired. Existing practice guidelines for transgender care suggest a minimum of three months of psychotherapy or living full-time in the desired gender before receiving GAH and a minimum of 12 months of GAH before undergoing gender-affirming surgery (10,13).

On average, participants in our study answered only one out of five knowledge questions incorrectly, with the most commonly missed questions involving the details of fertilization (i.e. An egg from a person born female and a sperm from a person born male

are needed to make a baby) and the ability of physicians to accurately predict the effects of GAH on fertility. Taken together, our findings imply that transgender adolescents understand the overarching concepts of GAH and diminished fertility but may need additional discussion about the specific details of reproduction and expectations for their medical care. That these details of fertilization were unknown and expectations unclear in several patients on gender-affirming medical therapy further suggests missed opportunities for patient education that should be prioritized in this young population.

The most common source of information in our study was a physician (65%) or family and friends (52%). A much smaller percentage (32%) of participants had researched fertility topics online than the percentage of participants (92%) in a similar study by Strang *et al.* (97). The patient population was similar in both studies, but a relative paucity of online resources for information about transgender-specific reproductive health and fertility is available to the transgender community. Whereas the oncology community has a host of online resources supporting fertility planning (e.g., FertileHope.org, the Lance Armstrong Foundation/Livestrong, the Susan G. Komen Breast Cancer Foundation) (95,98), the transgender community has exceedingly limited access to reliable online information. For example, Wu *et al.* examined the website content of 379 fertility clinics listed on the Society for Assisted Reproductive Technology database; only 32% of websites had transgender-specific language (99). The lack of representation on fertility websites may lead transgender patients to believe that their reproductive needs are overlooked, neglected, or actively discriminated against. As a result, they may avoid seeking out and receiving appropriate fertility care.

A small minority (9%) of participants in our study reported having received no previous information about the impact of gender-affirming medical therapy on fertility despite receiving a GnRH agonist or testosterone at the time of survey completion. In our pediatric gender clinic, we routinely integrate discussions about risks to fertility from gender-affirming medical therapy and goals for future parenthood into every patient's readiness evaluation. Patients who express the desire to have future children are offered a referral to a reproductive endocrinologist and infertility specialist for further evaluation prior to initiating gender-affirming medical therapy. Our results indicate that this model of care is effective, as most participants report having fertility-related discussions with a YGP provider. It is possible that the few participants on gender-affirming medical therapy who reported not receiving this information simply did not recall that fertility preservation was discussed during readiness evaluation. The oncofertility literature described many young patients who are unable to accurately recall details of their medical and treatment history (100) or of fertility discussions with their providers (93,95). In a study by Gilleland *et al*., 41% of adolescent cancer survivors reported being unaware of their risks for infertility despite having documented discussions about reproductive health risks (101). Moreover, adolescents may prioritize other healthcare issues, further inhibiting their ability to retain knowledge about fertility risks. Cancer patients and their families prioritize achieving personal health over preserving fertility (80,81). Similarly, results from our studies and others (102) suggest that transgender patients prioritize their current transition over their future fertility.

The multidisciplinary nature of gender-affirming care may also complicate discussions surrounding reproductive health and fertility. Current Endocrine Society

guidelines recommend that gender-affirming care be provided by a multidisciplinary team (10), and access to such multidisciplinary clinics specializing in transgender care has expanded rapidly in recent years (11,103,104). Transgender adolescents seeking care at these clinics may see a wide variety of healthcare providers in the course of their transition—including pediatric endocrinologists, mental health providers, urologists and/or gynecologists—who may or may not collaborate on patient care. Published guidelines emphasize the importance of addressing fertility issues prior to the start of GAH, but do not specify under whose purview this discussion should fall (10,13,19). Many individual pediatric gender clinics have published information on treatment outcomes in their patient population but do not address their strategies for discussing reproductive goals and fertility preservation options (11,22,104). At the YGP, discussions about goals for future parenthood, the impact of GAH on fertility, and options for fertility preservation routinely take place with all patients at least twice: once with the mental health provider during the readiness evaluation, using a standardized interview form, and again with the pediatric endocrinologist prior to initiating GAH. Patients who desire further information are then referred to a reproductive endocrinologist for further discussion and potential planning for FP procedures. An alternative approach—one more likely to ensure that fertility-related discussions take place across a variety of clinical settings but is far more time-consuming for clinicians—is to address fertility and reproductive health risks at every patient encounter. Our data demonstrates that such discussions effectively increase patients' fertility knowledge and awareness. Repetition of this information over time may be an important factor in the prevention of missed opportunities for preservation of fertility potential and future regret.

4.2 Attitudes toward Future Parenthood

Overall, transgender adolescents did not place an emphasis on the importance of future parenthood. About one-third indicated that having a child someday was important and one-third were unsure. Participants were interested in non-biological forms of parenthood such as adoption or fostering three times more frequently than they were interested in biological parenthood. This preference for non-biological over biological forms of parenthood in transgender adolescents has also been observed in prior studies (56,57). For example, the previously discussed study by Strang *et al.* found that many transgender adolescents (56%) expressed a desire for future parenthood (biological or non-biological), but few (24%) reported that this desire was specific to biological parenthood (97).

Several explanations could be posited for this disinclination toward biological parenthood. The first is that adolescents do not prioritize biological parenthood because of their young age. This explanation may seem intuitive given that the average age of participants in our study was 16 years while the average age of first-time parents in the U.S. is 26 years (105). One could surmise that adolescents are too young to care about reproductive issues. However, adolescent oncology patients of a similar age have, in several studies, stressed the importance of fertility and biological parenthood (81,94). These findings imply that factor(s) other than age must also be playing a role in transgender adolescents' seeming lack of interest in biological parenthood.

We hypothesize that one of these factors is the stigma associated with transgender parenthood. This stigma was not specifically explored in our study, but much of the literature reports such stigma, including public opposition and scrutiny towards

transgender pregnancy and parenthood (106,107), refusal of reproductive services (108), and lack of knowledge and understanding by healthcare providers (109,110). Much of this stigma stems from the belief that children of transgender parents are negatively affected (106,111). While the literature on the long-term well-being of children with a transgender parent is sparse, current findings have shown no difference in outcomes. Over a 12-year period, Chiland *et al.* followed 42 children who were conceived via donor insemination and raised by an FtM parent and found no difference in development or quality of life between children of transgender and cisgender couples (112). In another study, academic performance and rates of depression and attention deficit hyperactivity disorder were no higher for children with transgender parents than for the general population (113). Thus, the stigma surrounding transgender parenthood exists despite evidence suggesting normal developmental, quality of life, and psychological outcomes for children of transgender parents.

A second factor affecting parenthood goals may be the gender dysphoria associated with achieving biological parenthood. Gender dysphoria as a deterrent to biological parenthood is supported by a notable finding from our study—namely, that preferences for some forms of parenthood differ significantly by birth-assigned sex. Birth-assigned females were most likely to be interested in adoption, whereas birth-assigned males were most likely to be interested in surrogacy. These results suggest that birth-assigned females who identify as male may see pregnancy as incongruent with their gender identity. Ellis *et al.* interviewed eight FtMs who had been pregnant and given birth. Several recalled an intense fear prior to conception that pregnancy would mean a return to their female identity (109). Similarly, birth-assigned males who identify as

female may view conceiving with a partner by insertive intercourse as an unwanted experience (54,108). Of note, Nahata *et al.* found no difference in preference for adoption between birth-assigned males and females in a cohort of 72 transgender adolescents. However, parenthood preferences of participants in the Nahata study were obtained retrospectively and not documented in 26% of the study population. Our study used a prospective approach to prompt transgender adolescents about their preferences for future parenthood, and all survey participants answered all questions about parenthood preference. Therefore, our findings are likely a more accurate reflection of the differences in parenthood preference between birth-assigned males and females.

The aversion that transgender adolescents feel towards the achievement of biological parenthood may resolve by adulthood, and transgender adolescents in fact acknowledge this possibility (97,102). de Vries *et al.* described the remittance of gender dysphoria and body image dissatisfaction after GAH (51). Therefore, if parenthood desires are linked to gender dysphoria, parenthood desires may change over time as gender dysphoria decreases. Adult FtMs in long-term relationships who have deliberately achieved biological parenthood via sexual intercourse and pregnancy (66,109) or ART (67) have described a decrease in gender dysphoria, reporting a newfound connection and purpose to their bodies. Taken together, the literature demonstrates that transgender adolescents may change their desire for biological parenthood in adulthood after transition, when they have stable partnerships and minimal gender dysphoria.

4.3 Reproductive Concerns

The present study found that transgender adolescents had fair levels of overall fertility concern. Few participants were concerned about the loss of their fertility potential with

gender-affirming medical therapy. Our findings are consistent with those of Lawlis *et al.,* who found that only 7% of 118 transgender adolescents expressed concern about fertility. Unsurprisingly, fertility was ranked 25th out of 31 possible concerns in the study sample (102). In contrast, the oncofertility literature reports high levels of fertility concern in adolescents following gonadotoxic therapy (94,101). We hypothesize that the difference between fertility concerns in adolescents with gender dysphoria and adolescents with cancer, both of whom receive potentially gonadotoxic therapies, reflects several differences in their respective medical treatments. One difference includes the urgency and timeline of medical intervention. Adolescents with a life-threatening malignancy may not have had time to consider their fertility desires or undergo fertility-preserving measures prior to starting chemotherapy or radiation. Therefore, their perceived lack of control over their fertility may contribute to higher levels of concern. On the other hand, transgender adolescents have much more control over the timing of their transition and any desired FP procedures. GAH may be delayed until the adolescent feels certain about their fertility desires. A larger time period exists for decision-making and fertility-preserving procedures if desired, thereby possibly leading to less distress about fertility potential. A second difference includes the degree of gonadotoxicity between cancer therapy and gender-affirming therapy. Adolescents with cancer—particularly those who are older, are treated with alkylating agents or irradiation to the abdominal or pelvic organs —are significantly more likely than their siblings to experience impaired fertility or sterility, or the inability to conceive without the aid of medical intervention, in adulthood (114,115). On the other hand, transgender individuals treated with testosterone, estrogen, or GnRHa have shown at least partially reversible effects in fertility, with

pregnancy FtMs and normal semen parameters in MtFs report after cessation of GAH (66,72). The possibility of the restoration of fertility after stopping GAH may lead many transgender adolescents to postpone decision-making about future fertility or to feel reassured about their fertility potential. Finally, many oncofertility studies focus on survivors who have completed treatment and have post-treatment feelings of regret and loss with respect to their fertility (87,88,95,101). Our study focuses on transgender adolescents who are at the beginning or the middle of transition; low levels of fertility concern may be secondary to motivation to complete transition.

In fact, one of the most commonly endorsed fertility concerns in our study included the postponement of transition to undergo FP. More than 1/3 of participants were concerned that undertaking FP would delay their transition, similar to findings of prior studies in which participants indicated concern about stopping GAH to achieve parenthood (54,79,109,116). We found no difference in level of concern based on use of gender-affirming medical therapy. That is, participants on GnRH agonists or GAH had similar concern about delaying transition to undergo FP as those who were not yet on gender-affirming medication. Thus, timely and continued receipt of gender-affirming medical therapy may be worth the risk of infertility for many transgender adolescents. Notably, and in contrast with our results, Nahata *et al.* found that only 1.4% of 72 transgender adolescents declined FP out of concern about delaying GAH. The conflicting results likely represent differences in data collection methods. The data from Nahata's study was abstracted in a retrospective manner from patient charts and therefore only reflects concerns that were mentioned and documented during routine patient

appointments. Had patients been specifically prompted about their concerns as in our study, the prevalence of concern about delaying GAH may have been higher.

Another concern commonly endorsed in our study was the time, stress, and effort required to become a parent. This concern was most frequently expressed by participants who indicated that future parenthood was unimportant and by participants in early adolescence. From this data we hypothesize that concern about the process of becoming a parent may deter some transgender adolescents, particularly the youngest patients who may overlook future parenthood, from pursuing fertility preserving measures. Therefore, young patients who express that future parenthood is unimportant may in fact need the most counseling to make a fertility decision that is based on careful consideration rather than fear or concern.

4.4 Unmet Information Needs

Our data showing that transgender adolescents have a basic understanding of reproductive health and fertility topics is consistent with our subsequent data showing low levels of perceived information needs. Over half of participants reported that they had all of the information they wanted about fertility topics. The level of perceived information need did not differ by parenthood desire or reproductive concern. For example, participants who did or did not view future parenthood as important or concerning felt similarly well informed about fertility topics. Therefore, our findings are likely a reflection of participants feeling content about the amount of information they have about fertility topics rather than a reflection of disinterest.

The informational requests most commonly cited in our study included options for FP and risks and benefits of delaying GAH to undergo FP. Similar results have also

been observed by Light *et al.* who found that requests for information about fertility options persisted even in FtMs who had already experienced pregnancy (66). Thus, FP topics are an area ripe for patient education from providers who care for transgender patients. The Children's Hospital of Pennsylvania addressed this specialized need for FP education by creating a centralized, hospital-wide FP care team to provide timely and comprehensive FP counseling. The team consists of a pediatric oncologist, nurse practitioner, and nurse coordinator who initially see all patients referred for fertility counseling and scan inpatient and clinic lists for patients who may be at risk for impaired fertility. For patients who express interest in pursuing fertility preservation procedures, a reproductive endocrinologist, psychologist, general surgeon and urologist facilitate the procedures and provide ongoing counseling and support. Part of the counseling process includes access to patient-centered educational videos (www.chop.edu/services/fertility-preservation-program) (117).

Surprisingly, the majority of our participants expressed interest in adoption or fostering, yet none requested more information about alternative family-building options. These findings indicate that transgender adolescents in our clinic receive adequate information and counseling about non-biological but not biological options for future parenthood. When discussing options for reproduction and parenthood in the context of gender-affirming medical therapy, healthcare providers must be cognizant not only of the developmental age and stage of the patient but also of the unique needs of a patient with a transgender identity. Rodriguez-Wallberg *et al.* examined the experiences of nine FtMs in Sweden undergoing FP to achieve biological parenthood. Participants described traditional illustrations of women with ovaries as offensive and preferred illustrations of

ovaries within a man's body (118). Recently, trans-friendly figures such as the "Gender Bear," (119) the "Gender Unicorn," (120) and the "Genderbread Person" (121) have been used to explain gender concepts to children. Similar visual aids sensitive to the gender identity and developmental needs of transgender adolescents may also be used to explain fertility topics.

4.5 Limitations of the Present Study

The present study has several limitations. Participants included a small sample of mostly birth-assigned females who identify as male (74%). Population-based studies have found that slightly more transgender individuals are birth-assigned male than are birth-assigned female. The lack of representation of birth-assigned males in our data, though reflective of the patient population seen in our clinic, limits the generalizability of our findings to the larger transgender population. In addition, most of the published literature on transgender reproductive health stratifies participants by gender identity (MtF, FtM, or gender non-binary). Our study sample had too few gender non-binary participants to assess the data by gender identity. Participants were thus stratified by birth-assigned sex rather than by gender identity. Additionally, our study did not include a control group. Inclusion of cisgender controls would allow for better identification of the potential differences in baseline knowledge and attitudes toward parenthood between transgender adolescents and their cisgender peers. Future studies should include a larger sample size of both transgender and cisgender adolescents across multiple institutions to yield more generalizable conclusions and allow for important comparisons by gender identity in future studies.

Other limitations are inherent to all cross-sectional survey studies. We were unable to provide additional details or clarifications about survey responses, such as how much of the concern related to FP or future parenthood was related to cost, or to follow participants over time. Additionally, we did not collect information about the relationship status of participants, which could have affected outcomes such as parenthood desires or fertility concerns. Future studies should collect this information and assess how attitudes regarding fertility and future parenthood change over time.

4.6 Conclusion

In summary, our work reveals that there are unique fertility-related needs among transgender adolescents in our clinic. Participants had basic knowledge about reproductive health and transgender-related fertility and were primarily interested in non-biological parenthood. Although overall reproductive concerns were low, those with the greatest levels of reproductive concern also placed the least importance on future parenthood. This data suggests that many transgender adolescents may deny the importance of future parenthood out of fear or concern. Future educational initiatives should focus on the risks for diminished fertility associated with GAH while mitigating concerns with information about the options for the preservation of fertility potential and pathways to future parenthood. Healthcare providers, as the main source of information in this population, are in a unique position to provide this information. Providers should assess parenthood desires and fertility concerns at every patient encounter to account for changes in priorities and information needs over time. Information gathered from our survey can be used to track patient preferences so that, when needed, healthcare providers can make timely referrals to fertility specialists and ensure patient satisfaction with

treatment decisions. Future studies may further this area of study by exploring the change in fertility-related attitudes over time and the role of regret in transgender adolescents who decline fertility preservation.

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6 Appendices

Appendix A. DSM-V Diagnostic Criteria for Gender Dysphoria in Adolescents and Adults[3]

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
   4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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[3] *Note*. From the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, Fifth edition. Copyright 2013 by the American Psychiatric Association.

Appendix B. Baseline Characteristics of Participants and Non-Participants

Sociodemographic variables were extracted from patient medical records and compared between participants and non-participants using an unpaired *t*-test for continuous variables and Fisher's exact test for categorical variables.

Participant Group	Participants (N=23)	Non-Participants (N=15)	P value
Age (years), mean ± SD			
Initial Presentation	16.0 ± 2.6	16.3 ± 2.8	0.74
Birth-Assigned Sex, n(%)			
Female	17 (74)	12 (80)	1.0
Male	6 (26)	3 (20)	
Gender Identity, n(%)			
Transgender Male	15 (65)	11 (73)	0.59
Transgender Female	6 (26)	2 (13)	
Gender Non-conforming	2(9)	2 (13)	
Race/Ethnicity, n(%)			
White/Caucasian	18 (78)	8 (53)	0.27[A]
Black/African-American	2 (9)	3 (20)	
Hispanic or Latino	2 (9)	2 (13)	
Asian	1 (4)	1 (7)	
Insurance, n(%)			
Public	8 (35)	5 (33)	1.0
Private	15 (65)	10 (67)	

[A] Caucasian vs. Non-Caucasian

Appendix C. Attitudes toward Future Parenthood: Sub-group Analyses using Fisher's Exact Test[A]

	P value					
		Biological Parenthood			Alternative Parenthood	
Participant Group	Future Parenthood Important	Self Bio Child	Partner Bio Child	Surrogacy	Adoption	Fostering
Sociodemographics						
Birth-Assigned Sex						
Female vs. Male	1.00	0.58	1.00	**0.04**	**0.04**	0.18
Age (years)						
12 to 14 vs. 15 to 17	0.26	0.57	1.00	0.25	0.60	0.63
12 to 14 vs. 18 to 22	0.52	1.00	0.55	1.00	1.0	1.00
Race						
Caucasian vs. Non-Caucasian	0.84	0.29	1.00	0.19	0.62	1.00
Insurance						
Public vs. Private	0.87	0.30	1.0	0.10	1.0	0.66
Transition Process						
Use of Puberty Blockers or GAH						
Yes vs. No	0.69	0.29	0.55	1.00	0.14	0.34

[A] All values listed are p-values comparing differences in frequency of important or yes responses by variables within participant groups. Bold numbers indicate a significant difference of $p<0.05$.

Appendix D. Reproductive Concerns: Sub-group Analyses using Analyses of Variance[A]

	P value						
	Subscales						
Participant Group	**Fertility Potential**	**Partner Disclosure**	**Child's Health**	**Acceptance**	**Becoming a Parent**	**Delaying Transition**	**Total**
Parenthood Desires							
Parenthood Important							
Yes vs. No vs. Unsure	**0.003**	**0.02**	0.84	0.06	**<0.0001**	0.15	0.45
Demographics							
Birth-Assigned Sex							
Female vs. Female	0.61	0.63	0.06	0.24	0.053	0.46	0.91
Age							
12-14 vs. 15-17 vs.18-22	1.00	0.27	0.84	0.51	**<0.0001**	0.47	0.40
Transition Process							
Use of Puberty Blockers or GAH							
Yes vs. No	0.89	0.34	0.26	0.68	0.58	0.46	0.73

GAH = gender-affirming hormones (testosterone or estrogen)

[A] All values listed are p-values comparing differences in reproductive concern scores by variables within participant groups.

Bold numbers indicate a significant difference of $p \leq 0.05$.