Assessing for Ovulation in Transmasculine Individuals on Testosterone: Implications for Unmet Need for Contraception in the Trans Community

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Abstract

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Importance: An estimated 1.4 million people in the United States identify as transgender or non-binary (TNB), signifying that their gender identity does not correspond with their assigned birth sex. Individuals assigned female at birth may seek gender-affirming hormone therapy with injectable testosterone. No studies have directly examined ovulatory function or contraceptive need in transmasculine individuals on testosterone.

Objective: Our objective was to determine whether testosterone reliably suppresses ovulation in transmasculine individuals, and to use this and existing data to perform an assessment of unmet need for contraception in this population.

Methods: This is a observational prospective trial based at a community clinic serving over 400 patients annually for gender affirming hormone therapy. We enrolled individuals who were assigned female at birth and are currently using or seeking to initiate masculinizing therapy with testosterone (transmasculine individuals). Over a 12-week study period, subjects collected daily urine samples for pregnanediol-3-glucoronide (PdG) testing and completed daily electronic bleeding diaries. We collected monthly serum samples for mid-dosing interval serum testosterone, estradiol and sex-hormone binding globulin (SHBG) levels, and anti-mullerian hormone (AMH) values at baseline and study end. Ovulation

was defined as PdG>5µg/mL for three consecutive days. We then used these data and the existing literature on fertility and family planning in this population to perform an assessment of unmet need for contraception.

Main Outcomes and Measures: Our primary outcome was the proportion of participants who ovulated during the study period. Secondary outcomes included predictors of ovulation such as age, length of time on testosterone, serum testosterone levels, body mass infex (BMI), and bleeding pattern.

Results: We enrolled 32 individuals and 20 completed the entire study. Median age was 23 (range 18-37). Six participants were new initiators of testosterone and 14 were continuing users. Among continuing users, median duration of testosterone therapy was 9 months (range 2-60 months). One participant-month of ovulation was observed using the standard criteria, however several other participants had transient rises in PdG followed by bleeding episodes suggestive of a dysfunctional ovulatory pattern. Significant research gaps exist in assessing for unmet need for contraception in the transmasculine population.

Conclusions and Relevance: This study suggests that testosterone rapidly induces ovulatory dysfunction leading to eventual ovulatory suppression, though intermittent ovulations may be possible even in long-term users. Contraceptive need is largely unrecognized in this community, and more data are needed.

Introduction:

Gender dysphoria refers to the distress or discomfort an individual experiences when their assigned birth sex is incongruous with the gender with which they identify. [1–3] Available treatment options for gender dysphoria include cross-sex hormone therapy and gender-affirmation surgery. Individuals may seek out one, both, or neither of these therapies in the course of their gender transition. [2–5] There is a broad range of identities and preferred terminology in this population. For clarity and consistency, we use the term "transmasculine individuals" to refer to individuals assigned female at birth who are seeking masculinizing gender affirmation care. It is estimated that there are 1.4 million transgender and non-binary (TNB) individuals in the United States. [6] Data suggest that the overall number of transmasculine individuals seeking hormone therapy is increasing. [7] Many transmasculine individuals seek hormone therapy without plans to proceed with eventual hysterectomy, [8-9] yet data on fertility and family planning in this population are exceedingly limited.

Much of the research assessing fertility in the trans community has focused on fertility-sparing options for those desiring a biological child. Contraception for those individuals not currently desiring fertility is often overlooked, frequently due to the incorrect assumption that transmasculine individuals are not having sex that exposes them to pregnancy or that they rapidly become infertile once testosterone therapy is initiated. In reality, it is common for transmasculine individuals to have cisgender male partners, and condom use is often sporadic in these encounters. [10–14] In addition to the potentially dysphoric aspects of pregnancy in the trans male population, testosterone is categorized as a teratogen. Therefore, gaining a better understanding of contraceptive needs of transmasculine individuals is an important research goal. Despite nearly universal amenorrhea within months of initiating testosterone therapy, unplanned pregnancies have been documented in transmasculine individuals, and some who stop testosterone to become pregnant have conceived prior to return of menses. [15,16]

No prior studies have assessed the presence of ovulation during testosterone use. Potential fertility during its use and after cessation are unknown. Assessment of hormonal cycles through measurement of urinary hormone metabolites is validated over a wide variety of medical conditions. [17–21] Daily measurement of urinary pregnanediol-3 alpha-glucuronide (PdG) specifically can be used to assess for evidence of luteal activity and has shown excellent utility for retrospective analysis of ovulation. [21,22] This is a noninvasive method of charting hormonal cycles and assessing participants longitudinally for evidence of ovulation. This prospective cohort study uses daily urinary PdG measurements over a 3-month period to assess for ovulation in transmasculine individuals on testosterone in order to determine whether testosterone reliably suppresses ovulation and determine characteristics of transmasculine individuals who ovulate while on testosterone. We then use the findings of this study to discuss the potential burden of unmet need for contraception among the trans and gender-nonconforming individuals on testosterone.

Methods:

Study Population

Participants assigned female at birth desiring masculinizing therapy with testosterone were identified at the time of clinic visit and recruited from a community clinic with 3 sites in a large metropolitan area. Subjects were eligible for the study if they had not undergone hysterectomy or oophorectomy, were currently on or initiating injectable testosterone therapy, and had monthly menses prior to the initiation of hormone therapy. Subjects were excluded if they used any form of hormonal contraception in the past 3 months, had received treatment with a gonadotropin-releasing hormone (GnRH) agonist, were currently using finasteride, or used topical testosterone. Given lack of previous data, the sample size was based on precision estimates (Table 1). Written informed consent was obtained from all participants. Study procedures were approved by the University of Washington Institutional Review Board (HSD 4261).

Data Collection

Screen and Enrollment Visit

At time of recruitment we administered a baseline survey to participants to collect demographic data, medical history, sexual history, menstrual history, fertility plans, and experience with fertility and contraception counseling. The survey was developed in conjunction with a TNB health expert and community member in order to ensure questions were appropriate and relevant to potential participants. Gender and sexual identity categories were free-text and then collapsed into categories for data analysis. Participants then had their blood drawn for testosterone, estradiol, sex-hormone binding globulin (SHBG), and anti-mullerian hormone (AMH). Subjects used weekly injectable testosterone cypionate at a dose of 50-100 mg. Future study visits were scheduled for the participants mid-dosing interval day (halfway in-between injections, 3 or 4 days after injection) at 4 weeks, 8 weeks, and 12 weeks. If participants could not make an appointment at that time, follow-up visits were moved forward by one week so that blood draws were consistently occurring on their mid-dose day. Follow-up visits were scheduled at the clinic or external lab site most convenient for the participant. Participants were provided with urine collection kits and detailed instructions for collecting and freezing daily urine specimens. For new initiators, there was occasionally a delay between recruitment into the study and initiation of testosterone; they were instructed to begin urine collection when they began testosterone injections and this was considered day 1 of their participation. Continuing users of testosterone were instructed to begin urine collection immediately following recruitment into the study.

Follow-up study visits

Each participant had three follow-up study visits, scheduled on the day of the week that was their mid-dose day. We made every effort to schedule these visits at 4-, 8-, and 12- weeks after study initiation; however, if participants were unable to make these days, or had to reschedule, they were rescheduled a full-week forward so that their blood draw remained on their mid-dose day. At follow-up

visits, participants who were able to come to a clinic site for their visit had their blood drawn for testosterone, estradiol, and sex-hormone binding globulin. They filled out a short online survey using the study tablet that asked about changes to their testosterone dosing and updates to their medical record. At each follow up visit, participants turned in their urine specimens collected since the last visit. Participants who had follow-up visits at an external lab received the same blood draw and filled out their survey at home. They turned in their urine specimens in the clinic after completion of the study.

The final study visit also included a blood draw for AMH and a supplementary survey soliciting study feedback.

Study Activities

Participants collected daily urine specimens for the duration of study enrollment. They were instructed to collect first-morning urine. If they forgot or this was not possible we asked for a collection as early as possible in the day. Subjects were given all materials to collect urine and store it in 2ml tubes in their personal freezer. Subjects received daily text message reminders to collect their urine and were given the opportunity to report any irregularities in their collection for that day, for example, a late collection. A daily bleeding diary was also collected by text message, and participants were given a paper bleeding diary to maintain as a back-up.

Medical Record Abstraction

Participants medical records were abstracted to confirm BMI, medical history, current medications, and testosterone dosing.

Data Management

Study data were collected and managed using REDCap electronic data capture tools hosted at the Institute of Translational Health Science at the University of Washington. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking

data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.[23]

Laboratory Analysis

Serum samples were collected and sent for analysis to LabCorp (www.labcorp.com). Testosterone, estradiol, and SHBG were analyzed via electrochemiluminescence immunoassay per LabCorp protocol. AMH was analyzed via electrochemiluminescence.

Urine samples were stored initially in participants freezers before being turned in to study staff. They were then stored at the University of Washington at -80°C until all specimens were collected and ready for analysis. They were shipped on dry ice to the Oregon National Primate Research Center where they were analyzed for urinary PdG using ELISA (Arbor Assays). Criteria for ovulation was defined as urinary PdG greater than 5µg/mL for 3 days.[21]

Statistical Methods

Our primary outcome was the proportion of patients who ovulate as defined as urinary PdG greater than 5µg/mL for 3 days. Our secondary outcomes were the proportion of months during which participants ovulate, AMH levels at baseline and 3 months, and correlation between ovulation and age, duration of testosterone use, BMI, and the presence of vaginal bleeding.

We computed the proportion of transmasculine individuals ever experiencing ovulation over the study period and the proportion of months in which ovulation was observed. We performed bivariate regression to determine the relationship between ovulation and secondary outcomes. We planned to perform multivariable regression analysis to identify predictors of ovulation such as serum hormone levels or BMI.

For assessing change in AMH with testosterone use, difference in AMH at baseline and 3 months was calculated for each study participant. Change in AMH among new initiators vs. continuing users was compared using unpaired 2-sample t-tests.

Data analysis was performed using R statistical software version 3.4.1 (2017 R Foundation for Statistical Computing) and Microsoft Excel Version 15.35 (2017 Microsoft).

Unmet Need Analysis

The World Health Organization defines unmet need for contraception as "those who are fecund and sexually active but are not using any method of contraception, and report not wanting any more children or wanting to delay the birth of their next child."[27] In the second portion of this study, we perform a literature review and analysis to assess unmet need for contraception in the transmasculine community. We conducted a PubMed search for articles related to transmasculine individuals, hormone use, fertility, sexual practices, contraception use, sexual practices, and family desires. Search terms included but were not limited to transgender, testosterone, contraception, sexual health, pregnancy, and family planning. Published review articles and editorials were consulted for primary sources. Included sources were then reviewed and data were extracted for outcomes relevant to standard unmet need outputs (Appendix 1, Appendix 2).

Results:

Baseline Characteristics

Thirty-two individuals were enrolled. Twenty-two participants completed at least one month of data collection and 20 completed the full study. Of patients who discontinued the study with known reason, one discontinued due to starting twice-weekly testosterone injections; the remaining participants discontinued due to difficulty making study visits or inability to complete study activities. Figure 1 shows participant flow through the study.

Baseline characteristics are shown in Table 2, for new initiators and continuing users of testosterone. The median age was 23 (18-34). Median BMI was 28.5 (17.9-63.7). Half of participants identified their gender identity as male (n = 16); transmasculine was the second-most common gender identity (31.3%, n = 10). The majority of participants were white (90.6%, n=29). The most common sexual identity among participants was bisexual/pansexual/queer (40.6%, n = 13), with an equal number of participants identifying as straight and gay/lesbian (28.1%, n = 9).

Just under one-third of participants (31.2%, n=10) reported having used contraception in the past, with the most common method being the oral contraceptive pill (28.2%, n = 9). Nearly one-third of subjects reported having sex that could put them at risk for pregnancy within the past 6 months (31.8%, n = 10). Though participants did report a desire to parent in the future (43.8%, n = 14), most indicated they planned to adopt or have a partner carry the child; none had desire or plans to carry a pregnancy.

Of participants who completed the study, 6 were new initiators of testosterone and 14 were continuing users. Among continuing users, median duration of testosterone therapy was 5.5 months (1-60). Median time to amenorrhea after starting testosterone was 3 months (0-20). Bleeding or spotting was noted by 37.5% of participants, on 5.6% of days.

Ovulatory Analysis

We collected a total of 62 participant-months of urine for PdG testing. Using our initial criteria of PdG greater than 5µg/mL for 3 consecutive days, we found only one ovulatory participant-month (1.6%). The participant who clearly met ovulatory criteria was a new initiator who ovulated 2 weeks after study initiation. However, we noticed that several other participants, including all new initiators, had transient rises in their PdG values not meeting criteria followed by an episode of withdrawal bleeding 2-5 days after their PdG dropped. We hypothesized that these may represent dysfunctional ovulations. Wanting to capture all possible ovulatory episodes, we then re-analyzed the data using a very conservative criteria of PdG greater than 3µg/mL for 2 days to determine ovulation. This increased

our ovulatory months to 8 participant-months (12.9%). In bivariate analysis using this more conservative criteria, baseline measures for age (p=.41) and BMI were not associated with ovulation (p=.36). Time since testosterone use was associated with ovulation, with those ovulating having on average 14 fewer months on testosterone prior to the start of the 3 months observation period (p=.05). Ovulation by duration of testosterone use can be found in Figure 2.

Mean change in AMH among new initiators over the study period was 0.66 (SD=0.94) and mean change in AMH among continuing users was 0.77 (SD= 0.96). This difference was not statistically significant (p=0.84). Change in AMH values among new and continuing users can be found in Figure 3.

Assessing Unmet Need for Contraception in the Trans Community

The concept of unmet need points to a gap between an individual's pregnancy intentions and his or her contraceptive behavior. An immediate limitation of applying this method to the TNB community is that this metric has traditionally only been measured among women in heterosexual partnerships (and often only married women); there is no unmet need metric for men. In the standard definition, individuals may fall under the categories of met need, unmet need, or no need. Among the TNB community, there is also a large component of unknown need; for example, the TOTS study was designed to address the unknown contraceptive need of transmasculine individuals on testosterone. Significant additional data will be needed before we can accurately identify which transmasculine individuals using testosterone for gender-affirming therapy need contraception. Sexual orientation and expression also result in shifting categories of need; for example, an individual who has both cis-male and trans-male partners may have no need for contraception in some sexual encounters and unmet need for contraception in others. Transmasculine individuals who are clearly in the "no need" category include those who have undergone hysterectomy or who never have sex that puts them at risk for pregnancy.

Calculating Unmet Need

Unmet need for contraception is calculated using household surveys in which married women of reproductive age answer a standard questionnaire. Participants are asked whether they are currently pregnant; whether they desire additional children and their desired birth interval; current contraceptive use status; current fecundity, pregnancy, and amenorrhea status for those not currently using a contraceptive; planning status of most recent pregnancy; and use of contraception at the time of last pregnancy. An example of standard questions and probes is presented in Appendix 1. Appendix 2 shows a standard unmet need calculation.

No study has assessed unmet need for contraception among transmasculine individuals in a standardized fashion, and few representative surveys of TNB individuals have been performed in the United States. Utilizing currently available data we attempt to characterize unmet need for contraception in the TNB community within the US, and discuss major gaps and future research directions. Figure 4 uses the World Bank model (Appendix 2) to attempt to calculate unmet need in the community of trans and gender-nonconforming individuals assigned female at birth (AFAB) using best available data and demonstrates the gaps in knowledge and research. Details on how we obtained each of the inputs is presented below.

TNB Individuals Assigned Female at Birth

In traditional calculations of unmet need, the denominator for calculations is currently married women. This represents several obstacles for translation to our community of interest. TNB individuals may partner with individuals of any gender identity and sexual orientation including those assigned male at birth (AMAB) and those AFAB. Additionally, types of sex and sexual partners may change over time. For the purposes of this metric, we will set our denominator as all AFAB individuals currently identifying as trans or gender non-conforming. For consistency with the rest of the above study we will refer to

these individuals as transmasculine individuals, though we acknowledge that not all will identify this way.

Data from population-based surveys place the number of transgender individuals in the US at 1.4 million, which may be an underestimate.[28] 1.2 million of those individuals are <65.[8] Though the limit of reproductive age is usually defined as 50, more granular data is not currently available. In the United States Trans Survey (USTS), the only nationally representative survey of TNB individuals in the United States, 62% of individuals identified as either trans men or trans women and 35% identified as gender non-conforming. Of those, 57% of trans individuals and 80% of gender non-conforming individuals had female listed on their birth certificate.[8] Using these numbers, our best-estimate of the number of transmasculine individuals of reproductive age in the United States is 760,000.

Contraceptive Use

Data on contraceptive use in the TNB community is extremely limited. In the TOTS study, nearly one-third of participants had used contraception (not including condoms) at some point in the past, however our numbers are not representative as participants were excluded if they were currently using hormonal contraception.

Much of the data regarding current use of contraception in the trans population focuses on condom use for HIV prevention. A needs assessment of trans individuals in Virginia found only 18.9% used condoms "always" with their primary partner.[29] A second study assessing HIV risk behaviors found 31.1% "always" using condoms for vaginal sex,[12] and a similar study based in New England found 43.8% of transmasculine individuals had had unprotected vaginal intercourse in the past year with a cis-male partner.[10]

Only two studies have looked quantitatively at contraceptive use in the trans community. One small retrospective study of transmasculine individuals found 42% of subjects were not currently using any contraception. Among those who were using a form of contraception, 38% were using condoms

(though only 70% of those were always using them), 19% had a same sex partner, and 4% had a partner who had undergone vasectomy. None were using a hormonal form of contraception.[13] A larger prospective study showed 60.1% of participants using a wider array of contraception including all forms of hormonal contraception except for the patch and ring. The most commonly used method was condoms (22.5%). Though this is the most rigorous data to date, it represents a convenience sample that is likely biased towards increased use of contraception.[16]

There are no current data available regarding use of contraception for pregnancy avoidance versus pregnancy spacing in this population.

Pregnancy and Amenorrhea

In traditional calculations of unmet need, pregnant and amenorrheic patients are included together for purposes of calculation. This is because in a highly fertile cis-female population, the primary cause of amenorrhea is pregnancy or postpartum status. In the trans community, the primary cause of amenorrhea is testosterone use. As this overlaps with hysterectomy status and types of sexual partners, we will include amenorrheic individuals in our calculation of fecundity, and will only include pregnant transmasculine individuals in this classification.

There are no large-scale data regarding numbers of transmasculine individuals who have experienced or desire pregnancy. One study that specifically recruited for transmasculine individuals interested in pregnancy recruited 3 pregnant individuals out of 197 participants overall (1.5%). As pregnancy in transmasculine individuals is rare, and for the purposes of calculating a single-time point analysis of unmet need, we will assume that statistically 0% of transmasculine individuals are pregnant at a given time.

Fecundity

Data is extremely lacking on fertility, or fecundity, among the trans male community. As we examined in the TOTS study, whether or not testosterone renders an individual infertile is a major

outstanding question in the literature. TOTS data and prior supporting studies suggest that individuals may ovulate even greater than a year after starting testosterone.[30] Whether this ovulation can lead to pregnancy remains to be seen. No pregnancies have currently been documented on individuals actively and regularly taking testosterone, however one pregnancy has been documented in an individual who was taking testosterone irregularly, and individuals have stopped testosterone for a planned pregnancy and conceived successfully.[15,16]

Many studies have documented consistent amenorrhea within six months of starting testosterone. The question of amenorrhea, therefore, becomes a question of how many AFAB individuals are on testosterone for gender-affirmation. In the USTS, 49% of individuals surveyed had been on hormones for gender affirmation. This was not broken down by masculinizing and feminizing hormones, but represents by far the largest and most representative data source available.[8] In the single prospective study looking at transmasculine individuals and contraception, 60% were on testosterone.[16] This number is likely to increase with time, as 78% of respondents in the USTS indicated a desire to be on hormonal therapy at some point.[8]

Excluding those who are amenorrheic from testosterone, the issue of fecundity largely comes down to how many individuals have undergone hysterectomy, and how many are having sex that puts them at risk for pregnancy. In the USTS, 14% of transmasculine individuals had undergone hysterectomy with an additional 57% planning hysterectomy "some day".[8] No large-scale data has examined the number of Transmasculine individuals partnered with cis-men or trans-women, or having receptive vaginal intercourse with partners who produce sperm. In several smaller scale studies, 50-89% of participants had had receptive vaginal intercourse in the past year with a partner who was a cis-man or a trans-woman.

It is impossible to use this data to determine fecundity among the transmasculine population. In addition to the unknown effect of testosterone on fertility, it is unknown how the populations of

individuals on testosterone, individuals who have undergone hysterectomy, and individuals having penetrative vaginal intercourse with sperm-producing partners overlap. These research gaps represent significant barriers to the ability to assess for unmet need for contraception in this population.

Desire for Future Childbearing

In the TOTS study, no participants were interested in bearing their own children. In the single study looking at pregnancy in Transmasculine individuals, 25% of participants were interested in future childbearing.[16] No other data exists regarding the proportion of transmasculine individuals potentially interested in future pregnancy.

Discussion:

The effects of testosterone on fertility in transmasculine individuals are unknown. This study supports a small but growing body of literature documenting the effects of testosterone on ovarian function and potential fertility, and is the first to look prospectively at ovulation in this population. We found that though all participants initiating testosterone likely ovulated in their first month, for many participants this appeared to be a dysfunctional ovulation with lower elevations in PdG, similar to what is seen in the perimenopausal period.[18,24] By the second month of testosterone, no participants had a rise in their PdG suspicious for ovulation. We found that only time on testosterone was associated with ovulation, however two continuing users of testosterone in our study had a single possible dysfunctional ovulation after 5 and 17 months of testosterone. Due to small numbers of ovulation events by our PdG criteria, we did not perform multivariable regression due to statistical instability. Further research with larger numbers of participants over more time is required to determine risk factors for persistent ovulation.

We hypothesize that the anovulation seen in the majority of our participants after initiation of testosterone is due to suppression of the hypothalamic-pituitary-ovarian (HPO) axis either by

testosterone itself or by estrogen resulting from aromatized testosterone. Lower levels of estrogen and higher levels of testosterone seen in our continuing users support the mechanism of suppression by testosterone. This contrasts with previous studies which have suggested that HPO suppression is rare.[25,26] One study found no difference in LH levels after 16 weeks of androgen treatment,[26] and another small study of 6 transmasculine individuals on testosterone found only one with suppressed LH and follicle-stimulating hormone (FSH).[25] These studies contained very small numbers of participants, and more research is needed to better elucidate HPG axis activity after testosterone initiation.

This study has several limitations. Primary among them is our small sample size. Additionally, we only tracked participants for 3 months; therefore, if participants are oligo-ovulatory, we may not have captured an ovulatory event during their study period and incorrectly assume that they are suppressed. When broken down into new initiators and continuing users, our numbers are even smaller, so drawing conclusions about these sub-groups is potentially problematic. Additionally, we took many samples over a small sample size, raising the possibility of erroneous associations. This study should be seen as hypothesis-generating, and may guide future, larger-scale studies which can better characterize testosterone's effect on ovulation.

Recent studies have shown that up to ¼ of transmasculine individuals are interested in bearing children in the future,[15] though none of our study sample reported interest in future pregnancy. Whether interested in future fertility or in preventing pregnancy, greater knowledge of testosterone's effect on ovulatory function is critical to providing proper care and counseling to transmasculine individuals initiating testosterone. Additionally, as testosterone is a teratogen, transmasculine individuals having sex that exposes them to pregnancy should always be counseled to use a reliable contraceptive method.

Calculating unmet need for contraception in the transmasculine community has many challenges. Many of the fundamental concepts used in the standard calculation either do not apply at all or must be rethought in this population. Even defining the baseline population is far from straightforward. From the current data we estimate that there are 304,000 AFAB transmasculine individuals not currently using any method of contraception, including condoms. However the data breaks down significantly in determining how many of those individuals are actually at risk for pregnancy due to lack of data.

Of course, a traditional study examining unmet need for contraception in any community would not rely on piecing together prior data, but would undertake a careful and systematic representative survey. The USTS, published in 2016, was the first attempt in the United States to obtain systematic data about this population. Though that study supplied us with some of this data, contraception was not discussed in that study. Additionally, lack of understanding of even the mechanisms of when and how transmasculine individuals on testosterone are at risk for pregnancy would limit the ability of even a carefully executed survey to obtain a reliable calculation.

The data presented in the TOTS study and subsequent discussion of unmet need for contraception in the transmasculine community demonstrates significant lack of knowledge and research in transgender health. More and higher quality data is required at every level from the lab bench to the public health arena. Future studies should focus on pregnancy and family building intentions, contraceptive use, and the effects of testosterone on the reproductive system.

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Table 1. Estimated frequency of ovulation and associated confidence interval.

	Confidence interval assuming X participants	
Number observed To ovulate	X=20	X=30
0	0.0% (0.0%, 28.2%)	0.0% (0.0%, 20.2%)
1	5.0% (0.7%, 28.2%)	3.3% (0.5%, 20.2%)
2	10.0% (2.5%, 32.4%)	6.7% (1.7%, 23.1%)
3	15.0% (4.9%, 37.6%)	10.0% (3.3%, 26.8%)
4	20.0% (7.7%, 42.8%)	13.3% (5.1%, 30.6%)

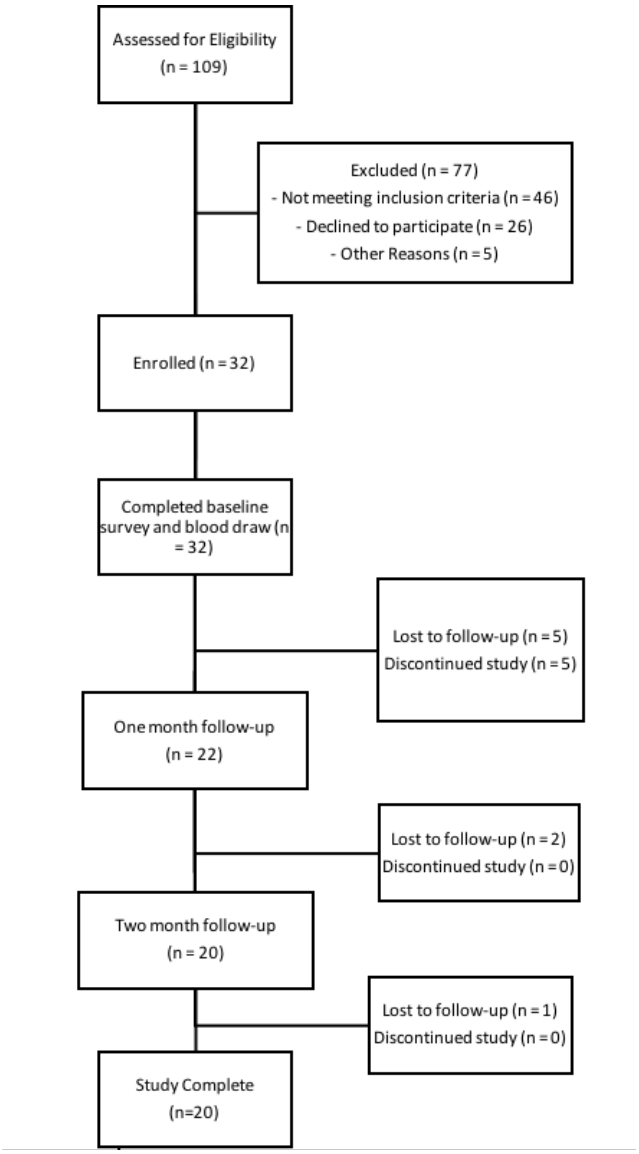


Figure 1. STROBE Study Flow Diagram

Table 2. Baseline Characteristics of Study Participants

Characteristic Median (range) or Count (%)	**All** (n=22)	**New Initiators** (n=6)	**Continuing Users** (n=16)	**p-value***
Months on testosterone	4 (0, 60)	0 (0, 0)	9 (2, 60)	--
Route of testosterone Intramuscular (IM) Under the skin (SQ)			 4 (25%) 12 (75%)	--
Age	23 (18, 37)	22 (18, 34)	23 (19, 37)	0.87
BMI	31 (19, 64)	26 (19, 42)	34 (20, 64)	0.52
Regular menses prior to testosterone	22 (100%)	6 (100%)	16 (100%)	--
Lab measures at baseline				
Testosterone	369 (19, 834)	31 (19, 49)	622 (63, 834)	<0.0001
AMH	3.3 (1.3, 10.5)	3.6 (2.5, 8.7)	3.0 (1.3, 10.5)	0.80
Estradiol	37 (12, 88)	53 (45, 88)	33 (12, 59)	0.002
SGBH	32 (10, 84)	61 (34, 84)	24 (10, 61)	0.002

* p-value is either for t-test or for chi-square test comparing those not using testosterone prior to study

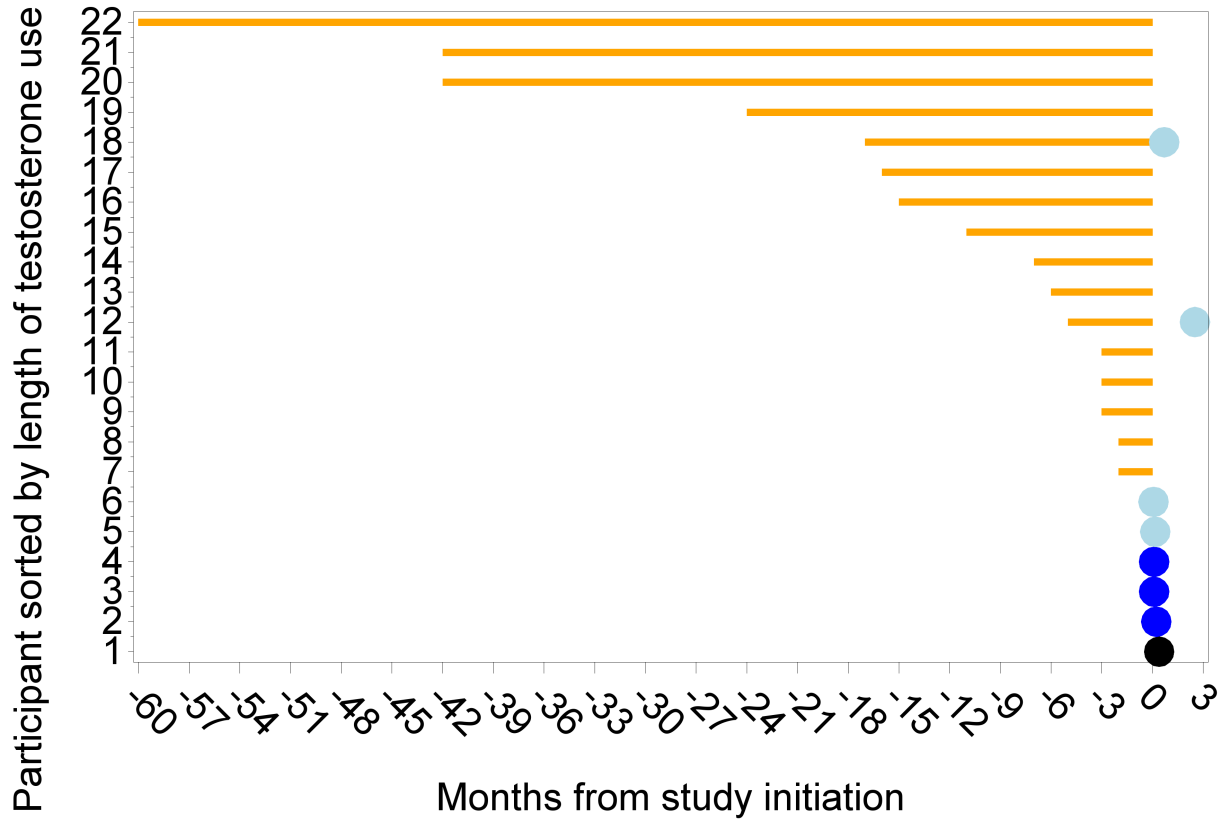


Figure 2. Ovulation by testosterone use. Orange lines show time on testosterone. Dots show ovulation: Light blue = ≥2 consecutive PdG measures above 3µg/ml, Blue = ≥3 consecutive PdG measures above 4µg/ml (with 2 of them above 5µg/ml) and Black = ≥3 consecutive PdG measures above 5µg/ml.

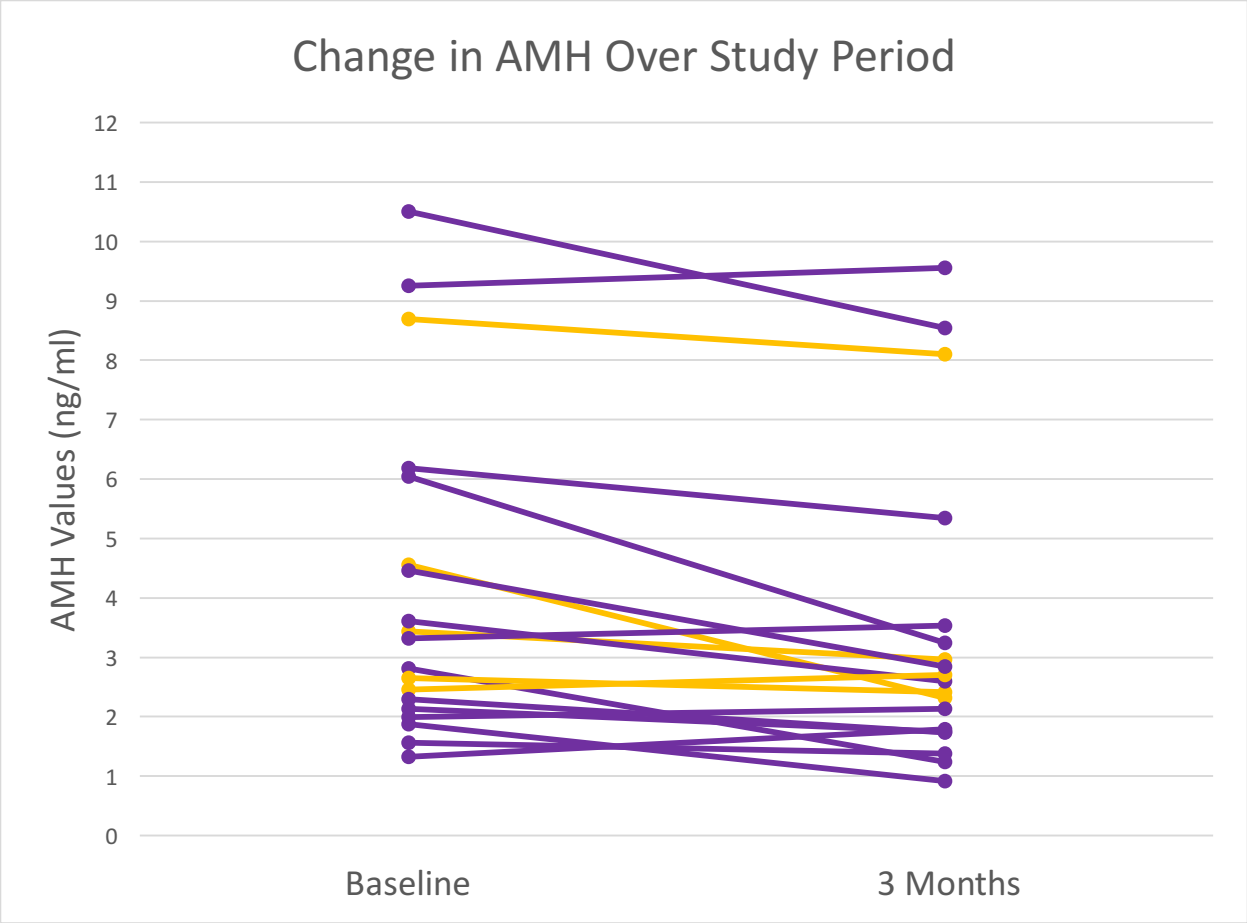


Figure 3. AMH levels over study time. Gold lines = new initiators. Purple bars = continuing users. No difference was found in change in AMH over study time between groups (p = 0.84)

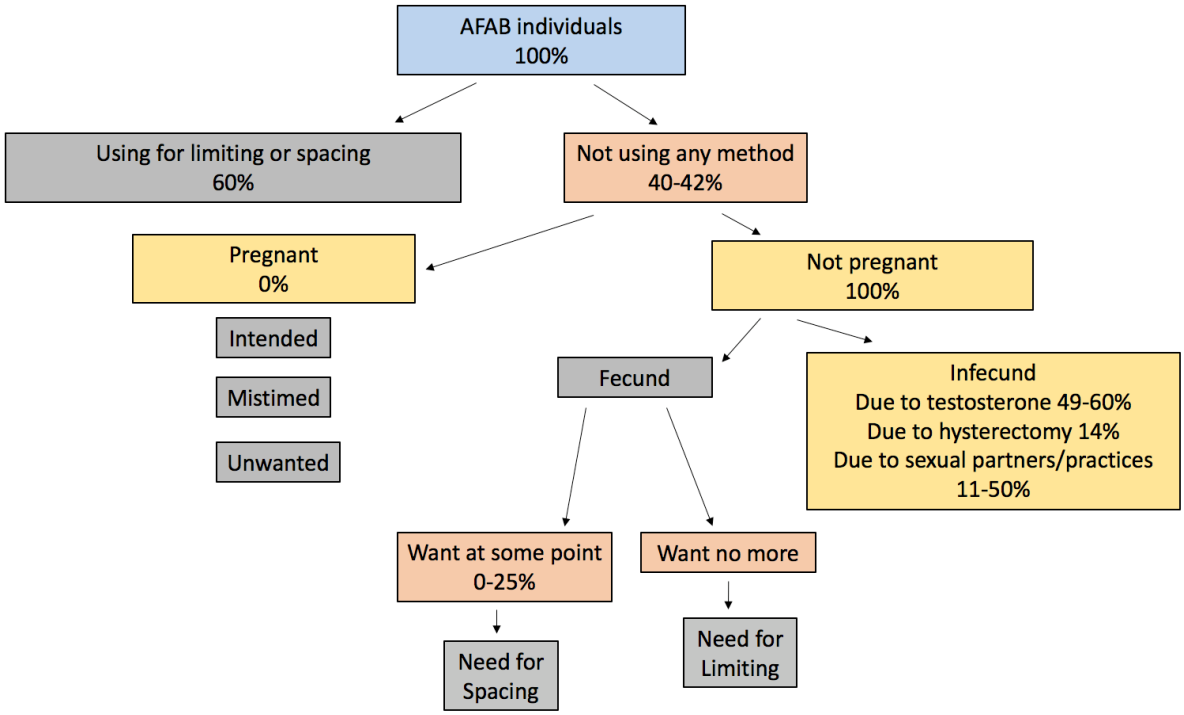


Figure 4. Calculating Unmet Need for Contraception. Blue boxes = data directly obtained from nationwide representative survey data. Yellow boxes = data extrapolated from nationwide representative survey data or good quality studies. Red boxes = data directly obtained from smaller or low-quality studies. Gray boxes = no data available. Percentages represent portions of all AFAB individuals.

Appendix 1. Standard questions for calculating unmet need for contraception**.** Source: Bradley, Sarah E.K., Trevor N. Croft, Joy D. Fishel, and Charles F. Westoff. 2012. Revising Unmet Need for Family Planning. DHS Analytical Studies No. 25. Calverton, Maryland, USA: ICF International.

Questions and Filters for Unmet Need Definition

Note that question text has been modified slightly from the DHS questionnaire to reflect the information needed for the definition of unmet need and avoid extraneous questions. Skip patterns have been modified to reflect the flow of questions in this set of questions. For the original questions and skip patterns, please see the DHS Model Questionnaire (Phase 6) (http://www.measuredhs.com/publications/publication-DHSQ6-DHS-Questionnaires-and-Manuals.cfm)

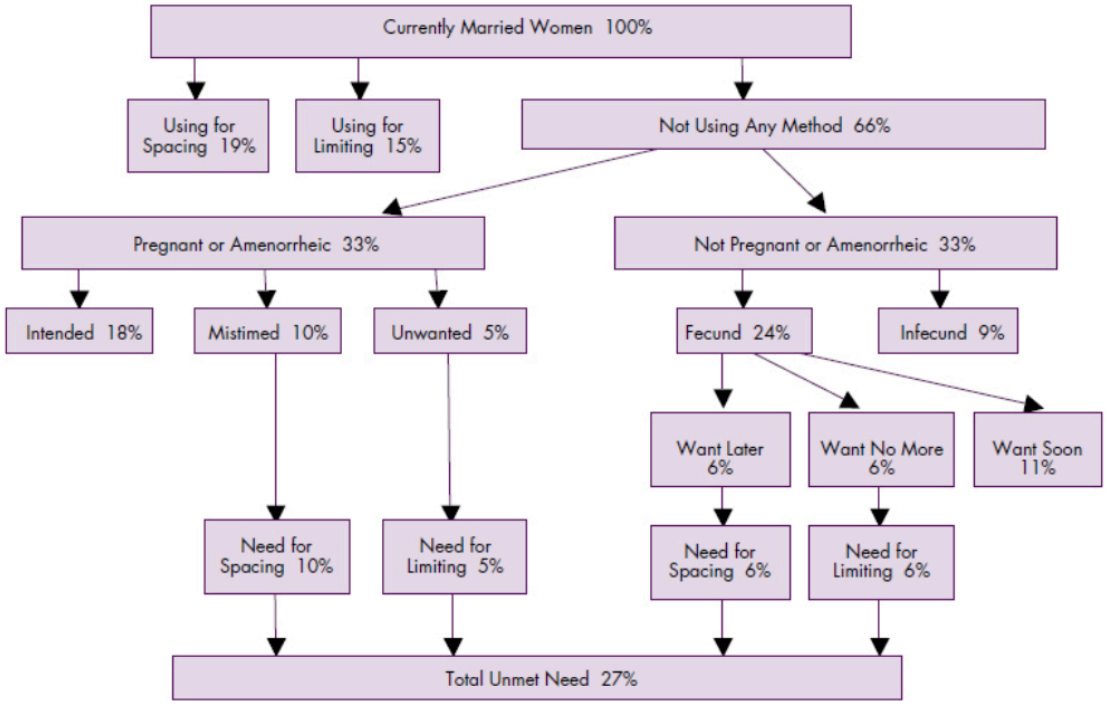
NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
226	Are you pregnant now?	YES . . . . . 1 NO . . . . . 2 UNSURE 8	→ 238
228	When you got pregnant, did you want to get pregnant at that time?	YES . . . . . 1 NO 2	→ 238
229	Did you want to have a baby later on or did you not want any (more) children?	LATER . . . . . 1 NO MORE 2	
238	When did your last menstrual period start? _____ (DATE, IF GIVEN)	DAYS AGO . . . . . 1 ☐☐ WEEKS AGO . . . . . 2 ☐☐ MONTHS AGO . . . . . 3 ☐☐ YEARS AGO . . . . . 4 ☐☐ IN MENOPAUSE/ HAS HAD HYSTERECTOMY . . . 994 BEFORE LAST BIRTH . . . . . 995 NEVER MENSTRUATED 996	
302	CHECK 226: NOT PREGNANT OR UNSURE ↓ ☐ PREGNANT ☐ → 313		
303	Are you currently doing something or using any method to delay or avoid getting pregnant?	YES . . . . . 1 NO 2	
313	Have you ever used anything or tried in any way to delay or avoid getting pregnant?	YES . . . . . 1 NO 2	
212	What name was given to your (last) baby? RECORD NAME	NAME _____	
215	In what month and year was (NAME) born? PROBE: When is his/her birthday?	MONTH . . . . . ☐☐ YEAR . . . . . ☐☐☐☐	

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
401	CHECK 215: BIRTH IN 2006 OR LATER BIRTH BEFORE 2006		→ 601
405	When you got pregnant with (NAME), did you want to get pregnant at that time?	YES . . . . . 1 NO 2	→ 447
406	Did you want to have a baby later on, or did you not want any (more) children?	LATER . . . . . 1 NO MORE 2	
447	Has your menstrual period returned since the birth of (NAME)?	YES . . . . . 1 NO 2	
601	Are you currently married or living together with a man as if married?	YES, CURRENTLY MARRIED . . . . . 1 YES, LIVING WITH A MAN . . . . . 2 NO, NOT IN UNION 3	
610	Now I would like to ask about your (first) (husband/partner). In what month and year did you start living with him?	MONTH . . . . . ☐☐ DON'T KNOW MONTH . . . . . 98 YEAR . . . . . ☐☐☐☐ DON'T KNOW YEAR 9998	
615	When was the last time you had sexual intercourse? IF LESS THAN 12 MONTHS, ANSWER MUST BE RECORDED IN DAYS, WEEKS OR MONTHS. IF 12 MONTHS (ONE YEAR) OR MORE, ANSWER MUST BE RECORDED IN YEARS.	DAYS AGO . . . . . 1 ☐☐ WEEKS AGO . . . . . 2 ☐☐ MONTHS AGO . . . . . 3 ☐☐ YEARS AGO . . . . . 4 ☐☐	
703	Now I have some questions about the future. After the child you are expecting now, would you like to have another child, or would you prefer not to have any more children?	HAVE ANOTHER CHILD . . . . . 1 NO MORE . . . . . 2 UNDECIDED/DON'T KNOW 8	→ 705 → END
704	Now I have some questions about the future. Would you like to have (a/another) child, or would you prefer not to have any (more) children?	HAVE (A/ANOTHER) CHILD . . . . . 1 NO MORE/NONE . . . . . 2 SAYS SHE CAN'T GET PREGNANT 3 UNDECIDED/DON'T KNOW 8	→ 707 → END
705	CHECK 226: NOT PREGNANT OR UNSURE How long would you like to wait from now before the birth of (a/another) child? PREGNANT After the birth of the child you are expecting now, how long would you like to wait before the birth of another child?	MONTHS . . . . . 1 ☐☐ YEARS . . . . . 2 ☐☐ SOON/NOW . . . . . 993 SAYS SHE CAN'T GET PREGNANT 994 AFTER MARRIAGE . . . . . 995 OTHER _____ 996 (SPECIFY) DON'T KNOW 998	→ END → END → END

NO.	QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
706	CHECK 226: NOT PREGNANT OR UNSURE ⚑ PREGNANT → END		
707	CHECK 303: USING A CONTRACEPTIVE METHOD? NOT CURRENTLY USING ⚑ CURRENTLY USING → END		
708	CHECK 705: NOT ASKED ⚑ 24 OR MORE MONTHS OR 02 OR MORE YEARS ⚑ 00-23 MONTHS OR 00-01 YEAR → END		
709	CHECK 704: WANTS TO HAVE A/ANOTHER CHILD ⚑ You have said that you do not want (a/another) child soon. Can you tell me why you are not using a method to prevent pregnancy? Any other reason? WANTS NO MORE/ NONE ⚑ You have said that you do not want any (more) children. Can you tell me why you are not using a method to prevent pregnancy? Any other reason? RECORD ALL REASONS MENTIONED.	NOT MARRIED ..... A FERTILITY-RELATED REASONS NOT HAVING SEX ..... B INFREQUENT SEX ..... C MENOPAUSAL/HYSTERECTOMY D CAN'T GET PREGNANT ..... E NOT MENSTRUATED SINCE LAST BIRTH ..... F BREASTFEEDING ..... G UP TO GOD/FATALISTIC ..... H OPPOSITION TO USE RESPONDENT OPPOSED ..... I HUSBAND/PARTNER OPPOSED ... J OTHERS OPPOSED ..... K RELIGIOUS PROHIBITION ..... L LACK OF KNOWLEDGE KNOWS NO METHOD ..... M KNOWS NO SOURCE ..... N METHOD-RELATED REASONS SIDE EFFECTS/HEALTH CONCERNS ..... O LACK OF ACCESS/TOO FAR ..... P COSTS TOO MUCH ..... Q PREFERRED METHOD NOT AVAILABLE ..... R NO METHOD AVAILABLE ..... S INCONVENIENT TO USE ..... T INTERFERES WITH BODY'S NORMAL PROCESSES ..... U OTHER _____ X (SPECIFY) DON'T KNOW ..... Z	

Appendix 2. Sample measurement of unmet need. Source: Westoff, C.F. 2006. New Estimates of Unmet Need and the Demand for Family Planning. DHS Comparative Reports No. 14. Calverton, Maryland, USA. Macro International Inc.

Figure 2. The Measurement of unmet need among currently married women, Zambia 2001–2002



Source: Westoff 2006.