Effects of Cross-Sex Hormone Replacement Therapy on Fertility in Transgender Patients: A Systematic Review

By
Arin Moriarty
Integrative Physiology, University of Colorado Boulder

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Thesis Advisor
Dr. Teresa Foley, Integrative Physiology

Defense Committee
Dr. Teresa Foley, Integrative Physiology
Dr. Alena Grabowski, Integrative Physiology
Dr. Pamela Harvey, Molecular, Cellular, and Developmental Biology

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Abstract

A growing area of research among the scientific community is the methods and effects of medical transition for transgender patients. One common component of medical transition is the administration of exogenous cross-sex hormones to patients to obtain a masculinized or feminized phenotype, referred to as hormone replacement therapy (HRT). There is limited research on much of these effects, including the effects of HRT on patients' fertility. In this study, I conducted a systematic review of research on the impacts of HRT on fertility, including calculating risk ratios and etiologic fractions. Thirty-nine papers were examined both qualitatively and quantitatively to assess the impacts of HRT on semen quality, ovulation, polycystic ovary morphology, and endometrial function. This study found that HRT reduces fertility in transgender patients, but not universally or completely; there is still evidence of fertility during HRT administration in many patients. Following discontinuation of HRT, reduced fertility will return to its pre-HRT status in most patients. This research will help clinicians counsel their transgender patients on fertility before and after their medical transition.

Terminology and Abbreviations List

Assigned female at birth (AFAB): Describes an individual who was assigned a female sex based on their external genitalia.

Assigned male at birth (AMAB): Describes an individual who was assigned a male sex based on their external genitalia.

Cisgender: Describes an individual whose gender identity aligns with their assigned sex.

Estrogen (E): The primary hormone involved in hormone replacement therapy (HRT) for AMAB individuals. Administration results in a more feminine appearing phenotype for these individuals.

Gender dysphoria: An experience of distress or discomfort brought on by a conflict between one's gender identity and sex assigned at birth. Gender dysphoria is experienced by many but not all transgender individuals.

Hormone replacement therapy (HRT): The process of administering one or more exogenous hormones to transgender patients to achieve a physical appearance more congruent with their gender identity. One component of medical transition.

Intersex: Describes numerous conditions in which sex development does not progress in a manner consistent with typical pathways of "male" or "female." Intersex infants are often coercively assigned a sex at birth, sometimes along with surgical intervention to mimic typical genitalia.

Medical transition: The process of undergoing medical treatments to change one's body to better align with one's gender identity. This could include hormone replacement therapy (HRT), voice therapy, laser hair removal, or surgeries such as mastectomy, genital reconstruction surgery, or facial feminization surgery. Many but not all transgender individuals undergo some form of medical transition.

Nonbinary/genderqueer: Umbrella terms for individuals whose gender identity falls outside of or is not confined to the established gender binary. These terms both fall under the wider "transgender" umbrella, but there are nuanced social, political, and cultural differences between them, and they are not interchangeable.

Testosterone (T): The primary hormone involved in hormone replacement therapy (HRT) for AFAB individuals. Administration results in a more masculine appearing phenotype for these individuals.

Transgender: Describes an individual whose gender identity differs from their assigned sex.

Transgender men: Individuals whose gender identity is male and who were assigned female at birth (AFAB).

Transgender women: Individuals whose gender identity is female and who were assigned male at birth (AMAB).

Introduction

Medical care for transgender individuals is a growing field in health care as broad cultural awareness and acceptance of diverse gender identity increases. A 2016 study by the Williams Institute reported that an estimated 0.6% of American adults, or 1.4 million individuals, identify as transgender (Flores, Herman, Gates, & Brown, 2016). Many of these individuals will pursue some form of medical transition in their lives. One common component of medical transition is hormone replacement therapy (HRT), where one or more exogenous sex hormones are administered to change a patient's hormone profile and therefore, the phenotype of some secondary sex characteristics. Hormone replacement therapy for transgender women or nonbinary individuals assigned female at birth (AFAB) involves administration of testosterone, which can cause physiological changes in the individual including hirsutism, amenorrhea, reduction of mammary gland tissue and fibrous connective tissue in the breasts, thickening of the vocal cords to cause a deepening and coarsening of the voice, and increased libido (Gooren & Giltay, 2008; Meriggiola & Gava, 2015a). Hormone replacement therapy for transgender men or nonbinary individuals assigned male at birth (AMAB) involves administration of estradiol and/or progesterone, sometimes in conjunction with androgen blocking medication. This results in physiological changes in the individual such as softening of the skin, breast development, fat redistribution to the hips and thighs, and decreased libido (Meriggiola & Gava, 2015b).

Many of the full-body effects of HRT are moderately well-researched and understood; however, research on the effects of HRT on fertility is lacking. Although testosterone therapy is known to cause amenorrhea, transgender men have been known to conceive while amenorrheic from testosterone use (Gooren & Giltay, 2008; Light, Obedin-Maliver, Sevelius, & Kerns, 2014). In AMAB individuals, HRT is thought to cause hypospermatogenesis and aspermia, but this does not occur in all patients and the long term effects and effects after cessation of HRT are not well-known (Meriggiola & Gava, 2015b). Surveys of transgender individuals indicate that this knowledge is relevant to the community, and that it is not well-discussed in clinical settings. A survey of 156 transgender and gender-nonconforming adolescents found that, although 62.2% either knew they wanted to have biological offspring, or were considering doing so, 82.7% of their health care providers had never discussed the possible effects of HRT on their fertility (Chen et al., 2018).

The human reproductive system is hormonally controlled by the hypothalamic-pituitary-gonadal (HPG) axis (Figure 1a). Gonadotropin releasing hormone (GnRH) produced in the preoptic area or arcuate nucleus of the hypothalamus travels to the anterior pituitary to stimulate gonadotrophs. In the pituitary, gonadotrophs produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Follicle Stimulating Hormone and LH travel through the blood stream to the gonads to stimulate the production of testosterone (T), estrogen (E), and inhibin. All of these hormones perform long-loop negative feedback on the hypothalamus and pituitary, and testosterone and estrogen both regulate reproductive function and secondary sex characteristics. Hormone replacement therapy impacts this system by raising the blood serum levels of testosterone and estrogen to abnormally high levels. Dosages of HRT are generally designed to achieve blood serum hormone levels comparable to those of cisgender counterparts.

In AMAB individuals taking HRT, high serum estrogen could result in reduced nutrients, growth factors, and proteins needed for proper sperm development and impaired release of mature spermatids (Figure 1c). Due to an isolating blood-testis barrier, only Sertoli cells and spermatogonia (stem cells) are affected by hormones in the circulation. Developing germ cells are only affected by hormone signaling from Sertoli cells. However, they could be indirectly affected by altered serum hormone levels through negative feedback mechanisms of the hypothalamic-pituitary-testicular axis. Increased serum estrogen could cause inhibition of hypothalamic GnRH production as well as FSH and LH production by the pituitary. Luteinizing hormone acts on Leydig cells to stimulate testosterone production within the testis. This testosterone and FSH from the pituitary act on Sertoli cells to regulate spermatogenesis, germ cell development, and spermiogenesis, development of proper morphology and motility in mature spermatids (Melmed, Polonsky, Larsen, & Kronenberg, 2012). Therefore, although high serum estrogen may not directly act on developing germ cells, it could still indirectly alter their developmental environment. Thus, it is reasonable to expect reduced sperm concentration, semen volume, motility, abnormal morphology, and impaired spermatogenesis in AMAB individuals taking HRT. As developing germs cells make up most cells in the testis, reduced testicular size would be expected as well.

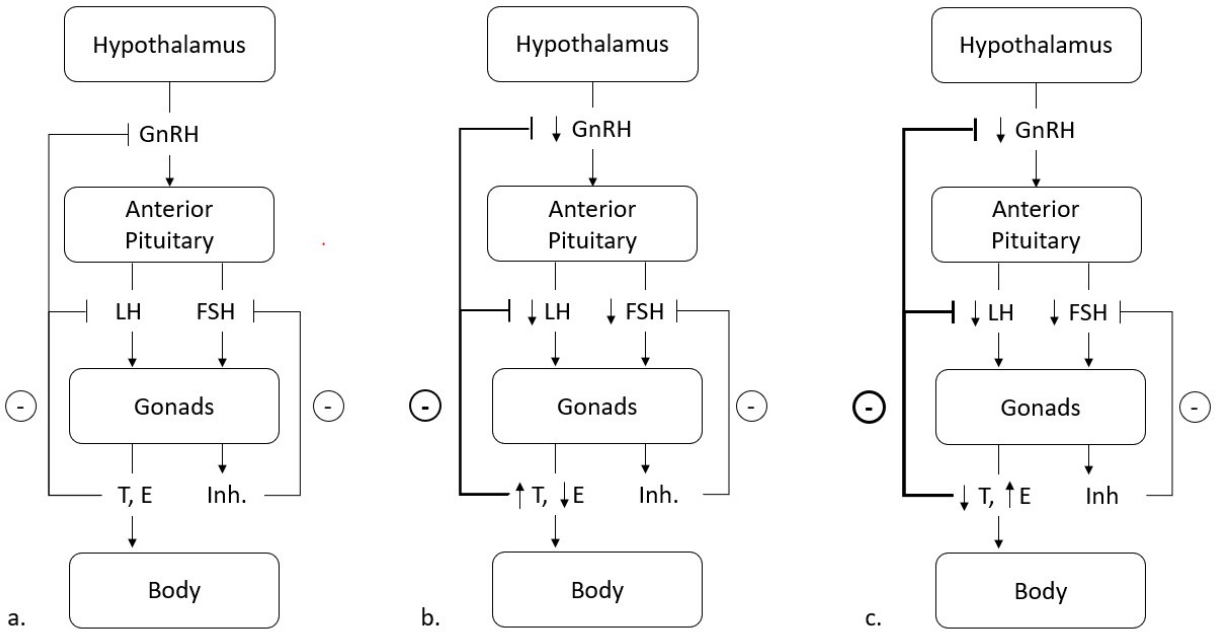


Figure 1: Diagram of the typical HPG axis (a), an HPG axis with interference by supraphysiological exogenous testosterone (b), and an HPG axis with interference by supraphysiological exogenous estrogen (c). Arrows between boxes indication stimulation and (-) indicates feedback regulation. Small arrows indicate increased or decreased hormone levels relative to baseline. Bold lines indicate increased strength of negative feedback.

Conversely, high serum testosterone in AFAB patients is less likely to disrupt the hormone cycles necessary for ovulation because of the intricacies of the feedback mechanisms (Figure 1b). Ovarian function is regulated by a complex hormonal cycle. During the follicular phase, FSH from the anterior pituitary triggers the development of a follicle in the ovary. It also causes granulosa cells to aromatize androgens, including testosterone, into estrogen, gradually raising the levels of estrogen and inhibin in the blood. Eventually, high estrogen triggers a spike in LH from the anterior pituitary which initiates ovulation. Following ovulation, during the luteal phase, the discarded follicle develops into the corpus luteum, which secretes progesterone and estrogen, inhibiting GnRH production in the hypothalamus. If a pregnancy does not occur, the corpus luteum degrades into the corpus albicantia. Presence of a corpus lutea and/or a corpus albicantia serves as evidence that ovulation is occurring in an individual. The ovarian cycle is regulated by a complex system of negative and positive feedback by estrogen on the hypothalamus. However, high testosterone in AFAB individuals taking HRT is not likely to affect this because testosterone does not directly perform negative feedback; it must be aromatized to estradiol first (Melmed et al., 2012). High testosterone could increase the rate of aromatization, but likely not enough to fully prevent ovulation. Additionally, since it is known to be possible for AFAB individuals to conceive while using HRT, ovulation must not be eliminated in all patients. Therefore, I would expect to see reduced evidence of ovulation in AFAB patients on HRT, but not a complete absence thereof.

One common reproductive disorder associated with high circulating testosterone is Polycystic Ovary Syndrome (PCOS), which is often associated with similar phenotypes to post-HRT transgender patients: hirsutism, amenorrhea or other irregular uterine bleeding, virilization, and anovulation. This is in part due to the high testosterone profile in patients with PCOS. Another key characteristic of PCOS is polycystic ovaries or polycystic ovary morphology (PCOM), where multiple follicles in the ovary develop simultaneously, resulting in ovarian cysts. This is due to low but constant secretion of FSH from the pituitary, which is characteristic of PCOS, continuously stimulating follicle development. However, there are numerous possible causes for PCOM besides PCOS. The specific defects causing PCOS and PCOM are not well understood and involve numerous complex negative and positive feedback mechanisms relating to altered gonadotropin and sex steroid levels as well as insulin resistance. Altered steroid hormone levels are generally thought to be an effect rather than a direct cause of the syndrome. Therefore, I would not expect to see significantly increased rates of PCOS or PCOM among AFAB HRT patients. Because of this, AFAB transgender fertility would not be significantly impacted by the effects of PCOM.

The uterus also undergoes a regular cycle in conjunction with the ovarian cycle. This cycle begins with menses, or the shedding of the endometrial lining through the vaginal canal. Menses is triggered by the sudden drop in estrogen and progesterone caused by the loss of the corpus luteum in the ovary. Following menses is the proliferative phase, where gradually increasing estrogen levels causes the build-up of new endometrial tissue. After ovulation in the ovary, progesterone from the corpus luteum promotes the maintenance of the endometrium and the start of the secretory phase of the uterine cycle. During the secretory phase, estrogen and progesterone from the corpus luteum causes the endometrium to secrete substances to maintain the uterine lining and support a growing embryo, should one be implanted. Secretory and proliferative endometrial states indicate that the uterus could be capable of maintaining a pregnancy should an embryo be fertilized and implanted in the uterus. An

inactive endometrium indicates that pregnancy may not be possible. The supraphysiological doses of testosterone associated with HRT have been shown to induce endometrial and cervical atrophy because of direct effects of testosterone on androgen receptors (ARs) on the uterus and cervix (Miller, Bédard, Cooter, & Shaul, 1986). Therefore, it is likely that AFAB patients undergoing masculinizing HRT will exhibit increased rates of inactive or atrophied cervix and endometrium.

Overall, I hypothesize measures of fertility in transgender patients on HRT to be reduced relative to cisgender controls, but not indicating an absence of fertility among the population as a whole.

Methods

Literature Search

A literature review of the biomedical database PubMed was performed from August 28, 2019 to October 17, 2019. Full search strings are available in Appendix A. For a study to be included, it must have met all the following criteria: performed on human subjects; written or available in English; free full text available, either through the publisher, CU libraries, or interlibrary loan; subjects were post-pubescent non-intersex adolescents or adults; included subjects identifying as transgender or nonbinary. Search results were assessed for relevancy to research based on their inclusion of transgender subjects on HRT, and assessment of one or more outcomes related to subjects' fertility. For potentially relevant articles, the full text was downloaded and further assessed for relevancy.

Data Analysis

Risk Ratios (RR) and confidence intervals (CI) were calculated for eight studies: six in AFAB subjects, and two in AMAB subjects. To be included in analyses, these studies needed to utilize a control group, clearly differentiate between results of subjects receiving versus not receiving HRT, examine more than a single patient, and provide categorical data. When necessary, the lead researchers for studies were contacted by email for additional data to use in the analysis. The RR measures risk, the probability of occurrence of an outcome. Statistically speaking, RR is a comparison between the chances of a specific outcome occurring in two different groups who have been exposed to different conditions. The RR is calculated using the following formula:

$$RR = \frac{Patients\ with\ outcome\ while\ using\ HRT}{(Total\ patients\ using\ HRT)} \Big/ \frac{Patients\ with\ outcome\ not\ using\ HRT}{(Total\ patients\ not\ using\ HRT)}$$

For this study, RRs and CI were calculated using an online calculator at http://vassarstats.net/odds2x2.html. If multiple control groups were used, as was the case in a few of the studies on AFAB transgender individuals, menstruating women were used as the control group for data analysis rather than menopausal women.

The CI is used to interpret the statistical significance of the RR. If the 95% CI includes the value "1," then the RR is not significant. This is because, in this case, the CI indicates that we cannot be more

than 95% sure that the RR accurately indicates whether the risk is reduced (RR < 1) or increased (RR > 1) by the change in condition.

Standard errors (SE) were calculated from CIs using the following equation derived by Dr. McQueen.

$$SE = \frac{\log(Upper\ CI) - \log(Lower\ CI)}{3.92}$$

The etiologic fraction (EF) indicates the proportion of the changes to a specific outcome that can be attributed to the treatment applied, which is HRT for the purposes of this study. The EFs were calculated using the following equation for all studies for which an RR could be calculated.

$$EF = \frac{(RR - 1)}{RR}$$

For outcomes which had a RR less than one, the EF calculated by this method is not meaningful, so an alternative etiologic fraction was (AEF) was calculated. For these cases, the RR was recalculated, reversing the definition of the "present" and "absent" conditions, resulting in a RR greater than 1. The AEF was then calculated using this alternative RR instead of the original.

Prevalence rates were calculated for various outcomes in all patients taking HRT in all studies: presence of a corpus lutea or corpus albicantia, endometrial activity, presence of endometrial polyps, polycystic ovary morphology, and spermatogenesis. This allowed for quantitative analysis of studies that didn't meet the criteria for calculation of a RR and EF. Prevalence rates were calculated using the following formula:

$$Prevalance\ rate = \frac{Number\ of\ patients\ with\ outcome\ while\ using\ HRT}{Total\ nuber\ of\ patients\ using\ HRT}$$

Additionally, the findings of all studies were examined qualitatively.

Results

Literature Search Results

During the literature search, 567 articles were screened for relevancy. Two hundred and twenty studies in non-humans were excluded and 347 human studies were screened for relevancy. Of these, 39 articles were determined to meet the criteria and were relevant to the research. These were primarily cohort studies, where participants were exposed, or not, to HRT, and then followed over time to compare the outcomes. Two potentially relevant articles were excluded because they didn't have a full text available, and one was excluded because it wasn't in English. Articles excluded for irrelevancy included those that assessed cisgender patients using hormone therapy for menopause, andropause, infertility, or cancer treatment; those that presented guidelines for clinicians interacting with transgender patients; and those that examined quality of life rather than specific fertility-related biomedical outcomes, among others.

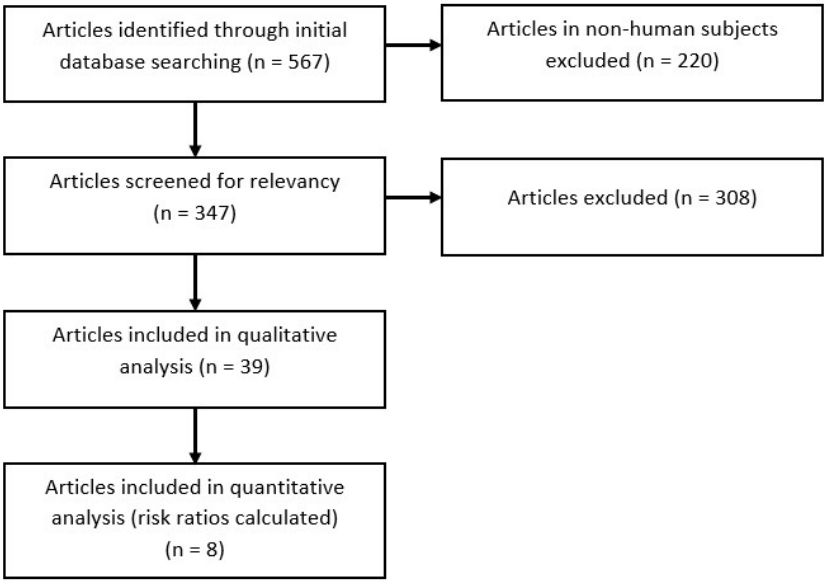


Figure 2: Overview of literature search process.

Results in AMAB Patients

Twenty relevant articles in AMAB patients were examined for this analysis (Table 1). Risk ratios, 95% confidence intervals, and standard errors were calculated for two papers in transgender women (Figure 3, Table 2). Data in this section is listed as "RR (Lower CI-Upper CI, SE)."

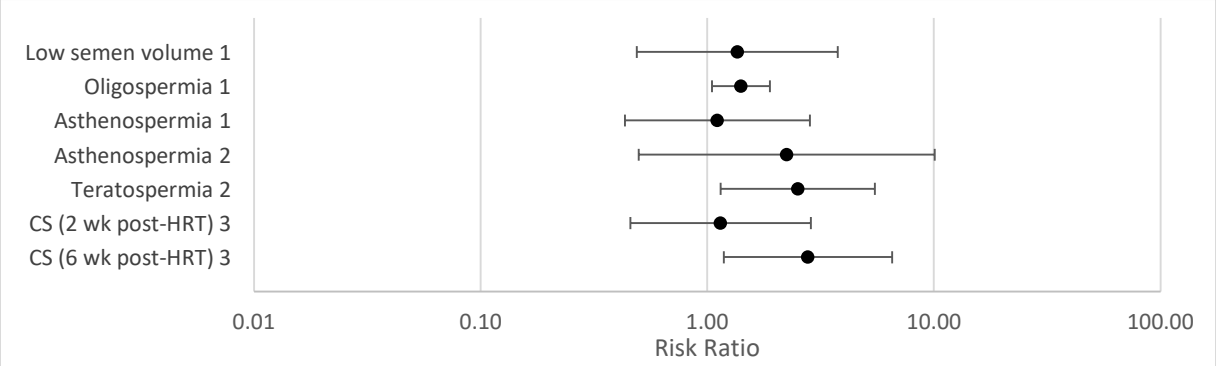
All of the RRs I calculated were greater than 1, which indicated increased risk of sperm abnormalities in transgender patients relative to cisgender controls. Using data from Li et al. (2018) which examined oligospermia (decreased sperm concentration), I calculated an RR of 1.406 (CI: 1.048-1.886, SE: 0.065) and an EF of 0.289. Additionally, I calculated a RR of 1.356 (CI: 0.488-3.766, SE: 0.226) and an EF of 0.262 for low semen volume based on data from the same study. Using data from Marsh et al. (2019), I found an RR of 2.505 (CI: 1.144-5.487, SE: 0.174) and an EF of 0.601 for teratospermia (abnormal morphology). When examining asthenospermia (reduced sperm motility) I calculated an RR of 1.106 (CI: 0.432-2.833, SE: 0.208) and an EF of 0.096 based on data from Li et al. (2018), and an RR of 2.237 (CI: 0.497-10.062, SE: 0.333) and an EF of 0.553 using data from Marsh et al. (2019). The latter study was notably done in pre-HRT transgender women. Based on results from Schneider et al. (2015a) comparing spermatogenesis post-HRT to current hormone users, I calculated an RR for comparing patients 2 weeks post-HRT to current users of 1.144 (CI: 0.458-2.859, SE: 0.203) and an EF of 0.126. When comparing patients 6 weeks post-HRT to current hormone users I found an RR of 2.778 (CI: 1.181-6.534, SE: 0.190) and an EF of 0.640s.

Table 1. Papers identified in literature review regarding AMAB transgender patients and their general findings.

AUTHORS	COUNTRY	OUTCOME(S)	SUBJECTS	RESULTS
Adeleye, Reid, Kao, Mok-Lin, & Smith, 2019	USA	Semen quality	28	No difference in sample volume between HRT, pre-HRT, and post-HRT subjects; significant differences between HRT and pre-HRT subjects in all outcomes; no difference between pre- and post-HRT subjects except in sperm concentration
Li, Rodriguez, Gabrielsen, Centola, & Tanrikut, 2018	USA	Semen quality	219	No difference in volume and motility between cis and transgender (pre-HRT) patients; otherwise, transgender samples lower quality than cisgender samples.
Lubbert, Leo-Rossberg, & Hammerstein, 1992	Germany	Semen quality	1	Sperm count decreased more quickly at lower doses than motility and volume. Normal values for motility 70 days post-HRT, volume 70 days post-HRT, and sperm count 100 days post-HRT. At high doses, no motile sperms identified after 50 days.
Marsh et al., 2019	USA	Depression, anxiety, stress, semen quality	39	Concentration, sperm count, normal morphology, volume, and TMC all lower in transgender women (pre-HRT) than cis men.
Rodriguez-Rigau, Tcholakian, Smith, & Steinberger, 1977	USA	Semen analysis, tissue histology	1	Low seminal volume, azoospermia, germinal cells mostly absent in tissue, with hyalinization and fibrosis of limiting membrane, interstitial area atrophy
Jindarak et al., 2018	Thailand	Tissue histology	173	Variety of states of spermatogenesis found, including 11% normal. Abnormality severity was not associated with age or duration of HRT.
Kent, Winoker, & Grotas, 2018	USA	Semen quality	135	4% of patients had normal spermatogenesis and 79% had none. No difference in duration of hormone therapy between those with and without evidence of some spermatogenesis.
Matoso et al., 2018	USA	Semen quality, tissue histology	50	Testis size normal in 86.8%, hypotrophic in 13.1%; aspermatogenesis seen in 80%, hypospermatogenesis in 20%. Reduced seminiferous tubule diameter relative to controls.
Nistal, Gonzalez-Peramato, & De Miguel, 2013	Spain	Tissue histology	11	Most patients showed pubertal-like maturation pattern. Higher doses of estrogen correlated with increased epithelial thickening and decreased lumen size of tubules.
Lu & Steinberger, 1978	USA	Semen quality, seminerous tubule examination	9	HRT subjects showed absence of Leydig cells, very few spermatogonia, occasional Sertoli cells with two nuclei, and osmiophilic lipid droplets and large vacuoles in Sertoli cells

Thiagaraj et al., 1987	Singapore	Semen quality, tissue histology	10	30% normal spermatogenesis, 60% absent.
Sapino, Pagani, Godano, & Bussolati, 1987	Italy	Immunohistochemical study	5	Found correlation between degree of atrophy and plasma hormone levels. No correlation with HRT duration. All patients had maturation arrest, absence of Leydig cells, and misshapen Sertoli cells.
Venizelos & Paradinas, 1987	UK	Testicular examination	5	No complete spermatogenesis. One case exhibited normal testicular size and reduced spermatogenesis. Others showed atrophy and marked hyalinization of the basement membrane.
Schulze, 1988	Germany	Testicular morphology	11	HRT caused small seminiferous tubules diameter, thickened lamina propria, misshapen spermatogonia and immature Sertoli cells.
Schneider et al., 2015	Germany	Hormone level, testicular weight, morphology	108	More complete spermatogenesis in patients 6 weeks post-HRT than 2 weeks post-HRT or current HRT, which are mostly maturation arrest.
Payer, Meyer, & Walker, 1979	USA	Spermatogensis, Leydig cells	9	Range of levels of atrophy/malformation present, no complete spermatogenesis present.
Kisman, De Voogt, & Baak, 1990	Netherlands	Leydig cells, Johnson score to quantify spermatogenesis	25	HRT increased interstitial tissue. Significant decrease in Leydig cells and lower Johnson score than controls. Effects of LHRH agonists and estrogen treatment likely reversible up to 18 months.
Chiu et al., 1993	Taiwan	Testicular histology	18	75% showed maturation arrest, 12.5% normal, HRT only affects spermatogenesis during puberty, or if started during puberty.
Barnard et al., 2019	USA	Semen parameters	12	Normal parameters pre-HRT. Post-HRT one patient normal parameters after 5 months, one patient azoospermic after 4 months.
Hamada et al., 2015	USA, Canada, Belgium	Pre-HRT Semen parameters	29	Pre-HRT patients showed high rates of oligozoospermia (27.5%), asthenozoospermia (31%), teratozoospermia (31%), and low TMC (68.9%).

Prevalence rates for varying levels of spermatogenesis were calculated based on data from nine studies (Figure 4). Of the patients in these studies, 67.7% had no spermatogenesis, 24.6% had reduced spermatogenesis, and 7.8% had complete spermatogenesis (Chiu et al. (1993); Jindarak et al. (2018); Kent et al. (2018); Matoso et al. (2018); Nistal et al. (2013); Payer et al. (1979); Rodriguez-Rigau et al. (1977); Thiagaraj et al. (1987); Venizelos & Paradinas (1987)).



[1](Li et al., 2018)

[2](Marsh et al., 2019)

[3](Schneider et al., 2015); CS = Complete Spermatogenesis

Figure 3: Calculated risk ratios of different outcomes measured in AMAB patients by study. Error bars depict upper and lower 95% confidence interval.

Table 2. Standard error and etiologic fractions for studies in AMAB subjects

AUTHORS	OUTCOME	SE	EF
Li, Rodriguez, Gabrielsen, Centola, & Tanrikut, 2018	Low semen volume	0.226	0.262
	Oligospermia	0.065	0.289
	Asthenospermia	0.208	0.096
Marsh et al. 2019[1]	Asthenospermia	0.333	0.553
	Teratospermia	0.174	0.601
Schneider et al. 2015	Complete spermatogenesis[2]	0.203	0.126
Schneider et al. 2015	Complete spermatogenesis[3]	0.190	0.640

[1]This study was performed in pre-HRT subjects

[2]Comparing patients that are 2 weeks post-HRT discontinuation to current HRT patients

[3]Comparing patients that are 6 weeks post-HRT discontinuation to current HRT patients

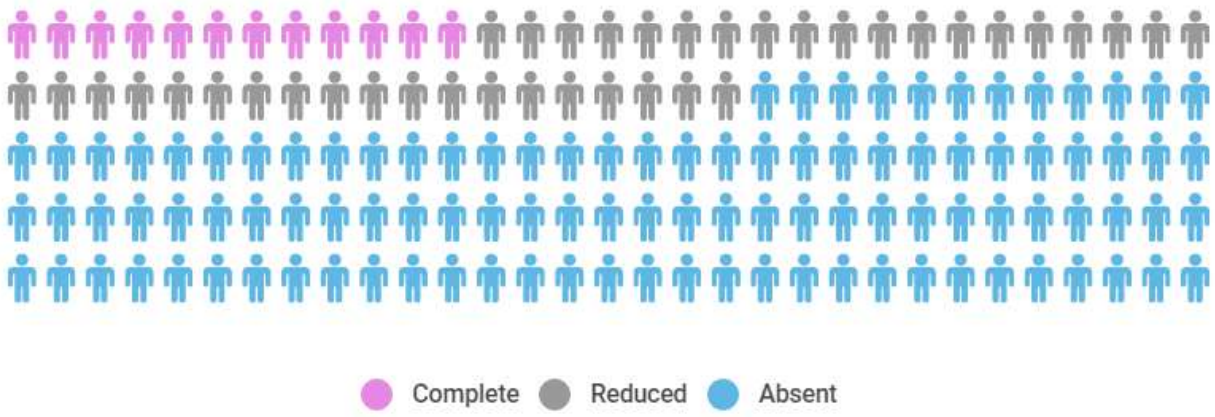


Figure 4: Calculated prevalence rates of observed complete, reduced, or absent spermatogenesis in the testes of AMAB transgender people taking HRT.

Results in AFAB Patients

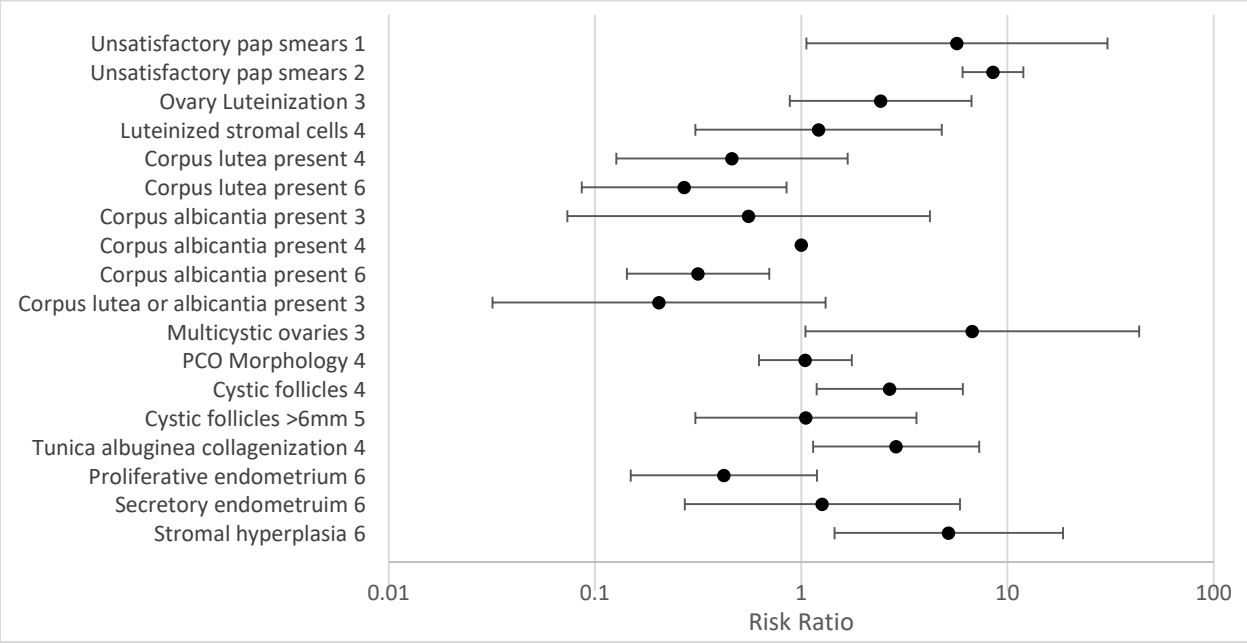
Nineteen articles in AFAB patients were examined for this analysis. Risk ratios, 95% confidence intervals, and standard errors were calculated for six papers in AFAB patients (Figure 5, Tables 4 and 5).

Several outcomes resulted in RRs greater than 1, indicating increased risk of the relevant outcome in transgender patients relative to cisgender controls. I calculated RRs for two papers which examined rates of unsatisfactory pap smears. Based on data from Adkins et al. (2018), I found an RR of 5.682 (CI: 1.057-30.539, SE: 0.373) and an EF of 0.824. Based on data from Peitzmeier et al. (2014), I found an RR of 8.489 (CI: 6.046-11.92, SE: 0.075) and an EF of 0.882. These studies were done primarily in pre-HRT patients. Additionally, I found an RR for ovary luteinization of 2.424 (CI: 0.88-6.68, SE: 0.225) and an EF of 0.587 based on data from Ikeda et al. (2013). Using data from Spinder et al. (1989) on luteinized stromal cells, I calculated an RR of 1.212 (CI: 0.306-4.799, SE: 0.305) and an EF of 0.175. Data from three studies indicated increased risk of multicystic ovaries: based on Ikeda et al. (2013), I found an RR of 6.75 (CI: 1.048-43.46, SE: 0.413) and EF of 0.852; based on Spinder et al. (1989), I calculated an RR of 1.046 (CI: 0.623-1.757, SE: 0.115) and an EF of 0.044 for PCOM in transgender patients and an RR of 2.684 (CI: 1.188-6.064, SE: 0.181) and an EF of 0.627 for cystic follicles; using data from Caanen et al. (2017), which counted cystic follicles larger than 6 mm, I determined an RR of 1.053 (CI: 0.306-3.621, SE: 0.274) and an EF of 0.0503. Based on Futterweit & Deligdisch (1985), I calculated an RR for secretory endometrium of 1.263 (CI: 0.272-5.868, SE: 0.34) and an EF of 0.208, and for stromal hyperplasia, an RR of 5.182 (CI: 1.447-18.563, SE: 0.283) and an EF of 0.807.

Several other outcomes had RRs less than or equal to 1, including several studies noting the presence of a corpus lutea and/or albicantia. Using data from two studies, Futterweit & Deligdisch (1985) and Spinder et al. (1989), noting the presence of a corpus lutea, I found an RR of 0.2707 (CI: 0.0863-0.849, SE: 0.253), an AEF of 0.505, an RR of 0.4615 (CI: 0.1269-1.6781, SE: 1. 0.286), and an AEF of 0.212, respectively. Three studies noted the presence of a corpus albicantia: I calculated an RR of 0.5556 (CI: 0.0734-4.206, SE: 0.449) and an AEF of 0.160 using data from Ikeda et al. (2013), an RR of

0.3158 (CI: 0.142-0.699, SE: 0.176) and an AEF of 0.774 using data from Futterweit & Deligdisch (1985), and an RR of 1 (CI: 1-1, SE: 0) with an EF of 0 using data from Spinder et al. (1989). In the latter study, all patients in both groups had a corpus albicantia, hence an RR of 1. Based on Ikeda et al. (2013), I calculated an RR for having either a corpus lutea or a corpus albicantia present of 0.2041 (CI: 0.0318-1.3102, SE: 0.412) with an AEF of 0.640. For the presence of a proliferative endometrium I found an RR of 0.421 (CI: 0.149-1.189, SE: 0.23) and an AEF of 0.367 using data from Futterweit & Deligdisch (1985).

Prevalence rates for evidence of ovulation were calculated from four studies in AFAB subjects (Figure 6). Among these, 8.7% of patients had a corpus lutea, 13.0% had a corpus albicantia, and 21.7% had one or both structures (Futterweit & Deligdisch (1985); Ikeda et al. (2013); Loverro et al. (2016); Miller, Bédard, Cooter, & Shaul (1986)). Prevalence rates for endometrial activity were calculated based on seven studies, and found that 2.22% of transgender patients had a secretory endometrium, 45.1% had a proliferative endometrium, 25.43% had an inactive endometrium, and 25.1% showed endometrial atrophy (Futterweit & Deligdisch (1985); Grimstad et al. (2019); Grynberg et al. (2010); Khalifa, Toyama, Klein, & Santiago (2018); Loverro et al. (2016); Miller et al. (1986); Perrone et al. (2009)). In five studies on PCOS morphology, 63% of patients showed PCOM (Futterweit & Deligdisch (1985); Grynberg et al. (2010); Ikeda et al. (2013); Spinder et al. (1989)). However, there was conflicting data: Ikeda and Pache (1992) both show no indication of PCOS morphology in transgender subjects.



[1](Adkins et al., 2018)
[2](Peitzmeier, Reisner, Harigopal, & Potter, 2014)
[3](Ikeda et al., 2013)
[4](Spinder et al., 1989)
[5](Caanen et al., 2017)
[6](Futterweit & Deligdisch, 1985)

Figure 5: Calculated risk ratios of different outcomes measured in AFAB patients by study. Error bars depict upper and lower 95% confidence interval.

Table 3. Papers identified in literature review regarding AFAB transgender patients and their general findings.

AUTHORS	COUNTRY	OUTCOME(S)	SUBJECTS	RESULTS
Light et al., 2014	USA	Survey on hormone use, pregnancy, birth outcomes	41	Many subjects became pregnant after discontinuing HRT or while still amenorrhoeic from HRT.
Gooren, 1985	Netherlands	Menstrual cycle phase length	8	HRT caused lengthening of follicular phase and shortening of the luteal phase. Ovulation appeared to still occur.
Adkins et al., 2018	USA	Pap smear results	11	Higher rates of unsatisfactory pap results than in age-match cisgender controls (13% vs. 0.5%).
Peitzmeier et al., 2014	USA	Pap smear results	3858	Higher rates of unsatisfactory pap results than controls (16.3% vs. 2.6%). More likely to have multiple inadequate tests.
Grynberg et al., 2010	France	Uterine and ovarian histology	112	99/224 ovaries appeared enlarged, 79.5% of patients (n=89) showed PCOM. 48% had proliferative endometrium.
Pache et al., 1992	Netherlands	Follicular fluid samples	35	The percent of healthy follicles and intrafollicular hormone levels did not differ between groups, smaller follicles observed in HRT patients.
Pache et al., 1991	Netherlands	Ovarian histology	30	HRT-treated ovaries showed more than double the number of follicles as cis women and more cystic atretic follicles. No difference in size or number of healthy follicles between groups. Stromal hyperplasia observed in all cases.
Ikeda et al., 2013	Japan	Ovarian histology	21	Androgen exposure caused thickening of ovarian cortex, stromal hyperplasia; one patient showed reduced LH and FSH. Two showed PCOM before HRT, but not PCOS. More atretic follicles than in controls, but not more of other types.
Amirikia, Savoy-Moore, Sundareson, & Moghissi, 1986	USA	Ovarian histology	16	HRT patients showed thickened tunica albinica and basal membrane relative to controls, comparable to PCOS patients. No evidence of recent corpus luteum. Number of follicles correlated negatively with age but did not vary between groups.
Spinder et al., 1989	Netherlands	Ovarian histology, LH secretion	44	LH and FSH decreased from baseline, LH interval and amplitude remained normal, 69% showed PCOM, 81% stromal hyperplasia.
Caanen et al., 2017	Netherlands	Ovarian morphology	136	Rates of PCOM not higher in FTM patients than in controls.
De Roo et al., 2017	Belgium	Ovarian histology	40	Normal distribution of follicle types in ovary. Extracted COCs largely developed correctly, with 87.1% normal spindle patterns.

Lierman et al., 2017	Belgium	Ovarian histology	16	Follicles harvested were usable for IVF, normal meiotic spindles in 90%. The number of COCs declined with age, increased with AMH. Maturation rate was comparable with literature.
C. De Roo et al., 2019	Belgium	Ovarian histology	6	Increased stiffness in outer ovarian cortex following T administration compared to controls.
Miller et al., 1986	Canada	Ovarian and uterine histology	68	Evidence of continued ovulation, no correlation with age or treatment duration. Cervical mucosal atrophy in 75%, 19% had atrophic endometrium, 81% had inactive endometrium.
Loverro et al., 2016	Italy	Ovarian and uterine histology	12	HRT does not induce endometrial atrophy. Observed active endometrium and multifollicular ovaries in 10 cases and secretive endometrium and corpus luteum in two cases.
Futterweit & Deligdisch, 1985	USA	Ovarian and uterine histology	31	74% transgender patients had histological features of PCOD. HRT did not induce endometrial atrophy.
Grimstad et al., 2019	USA	Uterine histology	94	Most patients had an active endometrium (69.1%). Endometrial thickness did not correlate with HRT duration
Perrone et al., 2009	Italy	Uterine histology	70	HRT did not stimulate endometrial proliferation but may induce atrophy. Histology was more similar to menopausal women than to age-matched menstruating women.

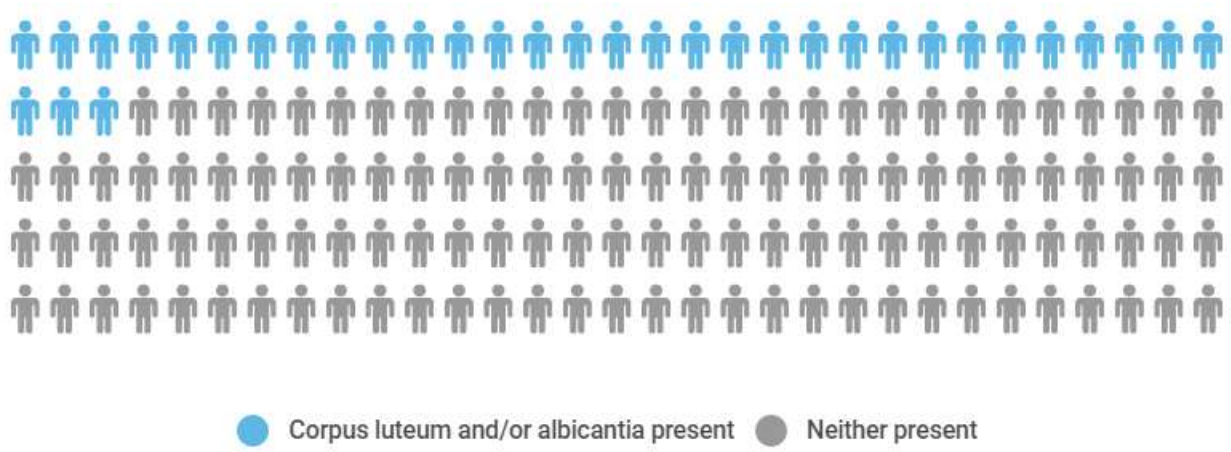
Table 4. Standard error and etiologic fractions for studies in AFAB subjects

AUTHORS	OUTCOME	SE	EF
Adkins et al. 2018	Unsatisfactory pap spears	0.373	0.824
Peitzmeier et al. 2014	Unsatisfactory pap spears	0.075	0.882
	Ovary Luteinization	0.225	0.587
Ikeda et al. 2013	Multicystic ovaries	0.413	0.852
	Collagenization of the tunica albuginea	0.205	0.653
	Luteinized stromal cells	0.305	0.175
Spinder et al. 1989	Corpus albicantia present	0	0
	PCO Morphology	0.115	0.044
	Cystic follicles	0.181	0.627
	Cystic follicles >6mm	0.274	0.05
Futterweit and Deligdisch 1985	Secretory endometrium	0.34	0.208
	Stromal hyperplasia	0.283	0.807

Table 5. Standard error and alternate etiologic fractions for studies in AFAB subjects

AUTHORS	OUTCOME	SE	AEF
Ikeda et al. 2013	Corpus albicantia present	0.449	0.160
	Either corpus lutea or corpus albicantia present	0.412	0.640
Spinder et al. 1989	Corpus lutea present	0.286	0.286
Caanen et al. 2017	Corpora lutea present	0.253	0.505
Futterweit and Deligdisch 1985	Corpora albicantia present	0.176	0.774
	Proliferative endometrium	0.23	0.367

a.



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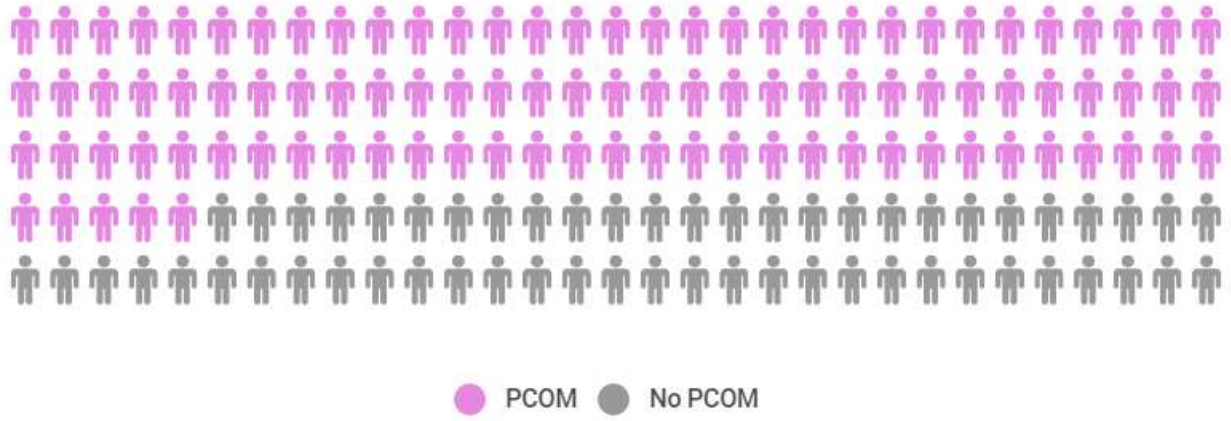

c.

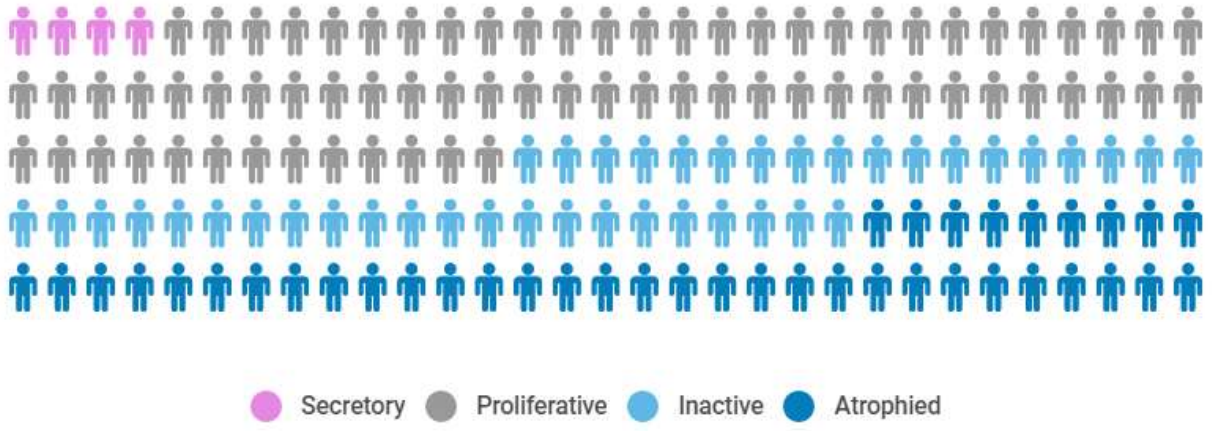

Figure 6: Calculated prevalence rates of evidence of ovulation (a), PCOM (b), and endometrial states (c) observed AFAB transgender people taking HRT.

Discussion

Effects in AMAB Patients

Although there is some disagreement between studies, semen quality in AMAB transgender patients currently using HRT appears to be significantly lower than in cisgender controls. Transgender patients were shown to have a statistically significant increased risk of oligospermia (decreased sperm concentration) and of teratospermia (abnormal sperm morphology) compared to cisgender controls. Based on my calculation from Li et al. (2018), patients on HRT were 1.406 times more likely than cisgender counterparts to exhibit oligospermia and 28.9% of the cases of oligospermia in AMAB patients taking HRT could be attributed to the HRT regimen (Li et al., 2018). Additionally, using data from Marsh et al. (2019), transgender patients were 2.505 times more likely than cisgender controls to display teratospermia and 60.1% of these cases in AMAB patients taking HRT could be attributed to the HRT regimen. Assigned male at birth patients on HRT also showed higher risk of significantly low semen volume and asthenospermia (reduced sperm motility) compared to cisgender controls; however, none of these changes in risk were statistically significant. These results are also supported by qualitative analysis of the existing literature. According to a case study comparing different HRT regimens in an AMAB patient, sperm count decreased more quickly at lower doses than motility and volume, suggesting that measures of sperm count or concentration may be more strongly impacted by HRT than other measures (Lubbert et al. (1992)). There was also a significant difference between HRT and pre-HRT subjects in all measures of semen quality, with transgender patients currently taking HRT exhibiting much lower semen quality than their cisgender counterparts (Adeleye et al. (2019)).

Across all studies included in this analysis, 67.7% of AMAB patients showed no evidence of spermatogenesis in their tissues, 24.6% showed reduced spermatogenesis, and 7.8% showed normal or complete spermatogenesis. However, there was significant variation between studies, with some showing no AMAB patients with normal spermatogenesis (Matoso et al. (2018); Payer et al. (1979); Sapino et al. (1987); Venizelos & Paradinas (1987)) and other studies showing as many as 30% of their AMAB patients with complete spermatogenesis (Thiagaraj et al. (1987).

Although there appears to be some disagreement about which specific outcomes are significantly impacted by HRT in AMAB patients, the consensus is that semen quality and spermatogenesis are negatively impacted by cross-sex hormone regimens. For transgender patients pursuing biological conception, this means that having biological children will be significantly more difficult than for cisgender men. However, none of these data definitively suggest that it is no longer possible to impregnate someone. A significant minority of patients (32.3%) still exhibited some degree of spermatogenesis and could theoretically cause a sexual partner to conceive in the absence of other birth control methods.

Effects in AFAB Patients

One of the most important factors in whether an AFAB individual can conceive is the presence or absence of ovulation. Evidence of ovulation in AFAB transgender individuals taking hormone replacement therapy were not necessarily significantly reduced. Risk ratios calculated from studies

regarding the presence of one or more corpus lutea and/or corpus albicantia were mostly statistically insignificant. My calculations indicated that transgender patients were 0.2707 times as likely to show a corpus lutea and 0.3158 times as likely to have a corpus albicantia as compared to cisgender counterparts. The effect of HRT accounted for 50.5% and 77.4% of these cases respectively. Across all studies that listed this data, 8.7% of transgender patients had a corpus lutea, 13.0% had a corpus albicantia, and 21.7% had one or both structures. There is no significant reduction of ovulation induced by HRT in transgender patients according to these studies. One study did, however, find that HRT in AFAB patients caused lengthening of the follicular phase of the ovarian cycle and shortening of the luteal phase but ovulation still appeared to occur (Gooren, 1985). This could indicate a shorter time period during with the AFAB individual would be able to conceive. Additionally, LH and FSH appeared to decrease from baseline following administration of HRT in transgender patients, but the LH release interval and amplitude remained normal, indicating that hormonal control of ovulation was likely not impacted by the HRT regimen (Spinder et al., 1989). Taken together, these data indicate that HRT does not necessarily negatively impact ovulation in AFAB patients.

One common concern regarding testosterone-based HRT in AFAB patients is the possible development of PCOM or other abnormalities with follicular development. Data within this review conflicts as to whether this is a legitimate risk. Calculations based on Ikeda et al. (2013) and Spinder et al. (1989) indicated that patients on HRT were respectively 6.75 and 2.64 times more likely to show some evidence of PCOM. Most of these instances (85.2% and 62.7%, respectively) could be attributed directly to the HRT treatment. Across all studies, 63% of AFAB patients showed PCOM. However, two other studies in this analysis show no significantly increased risk of PCOM in transgender patients (Caanen et al. (2017); Spinder et al. (1989)) and two studies show no indication of PCOM in any of their transgender subjects (Ikeda et al. (2013); Pache et al. (1992)) compared to controls. Additionally, data indicates that the meiotic spindles found inside the developing follicles appeared normal in 87-90% of cases, comparable with literature rates (Chloë De Roo et al. (2017); Lierman et al. (2017)). This also indicates normal follicular development leading to viable oocytes.

Hormone replacement therapy did not appear to result in endometrial atrophy in most AFAB patients. Assigned female at birth patients on HRT who were did not show significant change in their risk of atrophied endometrium or show a significant difference in the rates of secretory or proliferative endometrium compared to cisgender controls. Across all studies, only 25.1% of AFAB patients showed an atrophied endometrium, and 45.1% showed a proliferative endometrium compared to controls. Additionally, 7.74% of AFAB patients had endometrial polyps, indicating a possibly hostile gestational environment. These data indicate that while HRT may result in endometrial atrophy for some AFAB patients, this is not a universal effect, and many patients still show endometria such that conception would be possible.

Effects Following HRT Discontinuation

Following discontinuation of HRT in AMAB patients, sperm quality seems to largely return to pre-HRT levels. When comparing levels of spermatogenesis in patients 2- or 6-weeks post HRT

discontinuation to current HRT users, those AMAB patients who were 2 weeks post-HRT did not have significantly different levels of complete spermatogenesis than current HRT users; however, 6 weeks post-HRT, AMAB patients were 2.778 times more likely to show complete spermatogenesis than patients currently taking HRT. In 64% of cases showing complete spermatogenesis, the presence of complete spermatogenesis can be attributed to the discontinuation of HRT, based on data from Schneider et al. (2015a). Additionally, there was no difference between the semen quality of pre- and post-HRT subjects except in sperm concentration, which was lower in the latter group (Adeleye et al., 2019). These data indicate that semen quality return to baseline levels according to most measures in as little as 6 weeks post discontinuation of HRT in AMAB patients.

There is limited data on the fertility of AFAB patients following discontinuation of HRT. However, one study found in a survey that 61% of the subjects who had become pregnant had previously used HRT and 20% of these patients conceived while still amenorrhoeic from HRT (Light et al., 2014). It is also common knowledge within the transgender community that menstruation will resume if HRT is discontinued and that it will be possible to become pregnant post-HRT. Hormone replacement therapy in AFAB patients does not result in long-term infertility.

Duration of Therapy

One factor of note in this analysis is the duration of HRT relative to the effects noted in patients. Because HRT regiments are so variable, involving different combinations of medications at varying doses, it is extremely difficult to control for all the variables, and was not possible for my analysis. However, five studies, in both AFAB and AMAB patients, examined the correlation between duration of hormone therapy and the degree of impact on the measured outcomes. All of these studies found no correlation between degree of impact on outcomes and duration of HRT (Jindarak et al. (2018); Kent et al. (2018); Matoso et al. (2018); Miller, Bédard, Cooter, & Shaul (1986); Sapino et al. (1987)).

It is possible that this outcome is simply due to failure of the data; perhaps there is a relationship between duration and outcomes but there is too much variation between the physiology of different individuals as well as compounding effects of differing HRT regimens for a correlation to be detected. However, it is worth considering that, after the initial adjustment of the body to a new hormone profile, the physiology stabilizes, and there isn't any increasing severity of HRT effects over time. Hormone levels in patients on HRT are monitored over the course of the therapy, and dosages are adjusted to maintain hormone levels at what is considered typical for the target sex (i.e., maintain estrogen levels in AMAB patients at what would be normal levels for cisgender women). The goal is to keep these levels constant over time (Hembree et al. (2009)). It could be that once the body has normalized to these hormone levels, they stay constant enough that the physiology also stays constant over time, rather than continuing to be affected.

This would be good news for any transgender patients who begin considering the possibility of pursing conception after a long time on HRT, as it would necessarily be any less feasible at a later point in transition than if it had been pursued earlier. However, there is still very minimal data on this relationship, and although it is possible that there is truly no long-term relationship between duration of

HRT and degree of physiological changes, it is also possible that this relationship is simply not discernable with the data existing in the current literature.

Non-hormonal Factors

It is important to consider factors besides HRT that could result in reduced fertility in transgender patients. It was not possible for this analysis to control for possible confounding variables, but differences in fertility before initiation of HRT are important to consider. Many studies recorded baseline measures for their subjects, otherwise assessed pre-treatment parameters, or studied patients prior to initiating HRT.

Even before HRT is begun, AMAB transgender patients could have abnormal semen parameters relative to cisgender controls. In three different studies of pre-HRT transgender women, high numbers of the subjects exhibited oligospermia, asthenospermia, teratospermia, low total motility count (TMC), and/or low sample volume indicating lower semen quality prior to HRT initiation (Hamada et al. (2015); Li et al. (2018); Marsh et al. (2019)). There are multiple possible explanations for this. One possibility is that higher rates of mental health concerns among transgender women compared to cisgender controls could result in lower semen quality, a possibility supported by prior research (Durairajanayagam (2018)). Transgender women were found to have significantly higher rates of anxiety and stress than cisgender controls (Marsh et al. (2019)). Transgender women also reported higher rates of tucking and wearing tight undergarments, which could be associated with raising scrotal temperature and therefore lowering semen quality (Jurewicz et al. (2014)). However, this study did not find any correlation between these behaviors and semen quality. Two other studies, however, indicated that semen parameters of pre-HRT AMAB patients were all within normal limits (Adeleye et al. (2019); Barnard et al. (2019)). Although data is conflicting, is possible that lower semen quality found in this study could be the result of factors besides HRT and could be present in pre-HRT transgender patients as well.

In AFAB patients, it is possible that some endometrial or cervical changes found in patients could be the result of pre-existing conditions. In one study in this analysis, eight patients showed hirsutism before androgen therapy, and six of them later demonstrated PCOM upon ovarian examination. It is possible that this was a pre-existing condition in those patients and was not due to androgen therapy. Transgender patients also show evidence of cervical changes before HRT. In two studies of patients where the majority were not taking testosterone, my calculations showed that transgender patients have between 5.682 and 8.489 times increased risk of unsatisfactory pap smears compared to cisgender controls, where the results could not be determined and the patient would need to be retested. The majority of these cases (82-88%) could be attributed to the transgender identity of the subject. These results could be due to discomfort on the part of the patient or the health care provider, or could indicate a change in the cervix; a common noted cause of the failed result was reduced cellularity, or that not enough cells were collected for a definitive result. Taken together, these data could indicate non-hormonal reasons for changes in the endometria or cervix of AFAB patients.

Strengths and Limitations

This is the first broad systematic review of the effects of HRT on fertility in both AFAB and AMAB subjects. However, this study was limited in several ways. First, I was unable to perform meta-analysis. Relatively few studies met all the criteria for this type of analysis, because of failure to use controls, fully discuss the results of subjects in control groups, or because the sample sizes were too small to provide adequate data for a defined risk ratio. If a meta-analysis had been possible, it would have lent another dimension of statistical analysis to the data, improving the overall understanding of the overall findings of the research available.

Additionally, this study did not account for several important confounding variables such as specifics of individual HRT regimens, impacts and effects of HRT in intersex individuals, and possible impacts of medication non-compliance. There is a lot of variance in HRT regimens, as there are many versions of each hormone available. HRT in AMAB patients sometimes combine estradiol with other medications such as progesterone or an anti-androgen drug such as spironolactone. Additionally, the dosages of all these medications vary by the practices of the specific doctor and wishes of the patient and are often adjusted over time. Very few of the studies included in this analysis included detailed regimen data, as it can be difficult to acquire retroactively. Therefore, it wasn't possible to account for this factor in this study; however, the variation in regimen likely has a significant impact on the effects of HRT, so this is an important direction for future research.

As for intersex individuals, there simply isn't enough existing literature to support a broad review such as this one. Intersex conditions are fairly common, as high as 2% of live births, but are so varied that it is difficult to account for in an analysis of this level (Blackless et al. (2003)). However, this study would be more well-rounded and inclusive had it been possible to account for this population. Future research should consider the impact of HRT on the physiology of intersex patients.

Another important variable that was not considered in the study is the possible effects of medication non-compliance among the patients. Hormone replacement therapy can be extremely difficult to access financially and psychologically for many patients, and it is common to temporarily pause treatment without doctor supervision because the medication isn't affordable, because self-injections can be difficult to perform, or because the patient lost access to their prescribing physician. These lapses in treatment, however brief, will increase fluctuation of hormone levels in patients on HRT and potentially affect the physiology of the patient and overall effects of the treatment. However, the rate of non-compliance can be difficult to assess as many patients will be hesitant to report it, and none of the studies in this analysis reported incidents of medication non-compliance. However, this is an important topic for future research as barriers to treatment access remain in place in society.

This study also had several strengths. This is the first broad study to examine the effects of HRT in human subjects in both AFAB and AMAB individuals, across a variety of outcome measures, representing a novel perspective on this topic. Previous research has primarily focused on only AFAB or only AMAB subjects, and potentially missed connections or overlap between the two. Analyzing both of these groups allowed for a broader picture of transgender fertility from multiple sides. This is also the first broad literature review on this topic to calculate and discuss etiologic fractions, and to use this type

of epidemiological analysis for this analysis. The use of etiologic fractions allows for a deeper understanding of the extent to which the noted outcomes are due to the HRT regimen, and how much may be due to confounding variables. This deepens the analysis and improves our understanding of the complexity of these physiological systems.

Another strength of this research is that it makes the existing data and scientific understanding of these phenomena accessible to clinicians and to transgender people, so that the data are more easily communicated to patients and applied in real life decision-making. As noted in the introduction, 82.7% of transgender patients seeking HRT services reported that their health care providers had never discussed the possible effects of HRT on their fertility (Chen et al. (2018)). Based my experience within the transgender community, it is also common for providers, when discussing fertility while using HRT, to tell their patients (incorrectly) that they won't be able to conceive while using exogenous hormones. This lack of information and misinformation by providers can lead transgender people to make uninformed decisions regarding their fertility, hormone use, and birth control use. This review of existing research makes the scientific understanding of fertility on HRT more accessible to health care providers, so that they can accurately counsel their patients on how HRT may affect their fertility, so that patients can more easily make informed decisions about their bodies.

Additionally, this is the only study that I know of that focuses on the effects of HRT, or any other aspect of medical transition, on transgender patients, that was authored by a transgender researcher. This assumption could be incorrect, however, my own experience in transgender communities gives me additional insight into the practical effects of HRT as experienced by individuals, as well as into the intra-community perception of hormonal transition. It informs my understanding of the limitations of this research, from the complexity of HRT regimens to the difficulty of access within the community. It also informs a more broad and accurate use of language; the majority of the papers this study draws from used restrictive, othering, or incorrect language for their patients, such as continuously misgendering them or assuming their results only applied to or affected binary transgender individuals. The inclusion of nonbinary and genderqueer patients, as well as treating subjects with respect and understanding regarding their gender identity, is an important component of ethical research into transgender experiences. It not only makes said research more accessible to transgender readers who are impacted by these topics, it establishes the transgender community as worthy of respect within the scientific community. Research into transgender bodies is not complete without an understanding of transgender communities. This insight adds another dimension to the physiological analysis shown here and strengthens the research.

Conclusions

There is a shortage of data on the effects of HRT on the fertility of transgender individuals, and what data does exist is often conflicting or inconclusive. The data we have indicates that fertility may be somewhat, but not completely reduced in transgender patients. Effects of HRT do not appear to increase past initial changes to cause more significant changes with increased duration, and HRT does not result in long term loss of fertility; following discontinuation of the medication normal fertility should return in most patients. However, there is some possibility that reduction in semen quality in

AMAB transgender patients could be present prior to HRT, and therefore related to other factors such as stress and anxiety. Transgender patients hoping to avoid pregnancy should use birth control methods and not consider their HRT regimen to be a substitute for birth control. Transgender patients hoping to conceive should be able to do so but may wish to consider discontinuing HRT to raise their chances. Transgender patients who were assigned female at birth will have to discontinue HRT use to sustain a healthy pregnancy.

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Appendix A: PubMed Search Strings

Search 1:

("sex reassignment" OR “sex change” OR "gender change" OR "gender reassignment" OR "cross-gender" OR “cross-sex” OR transgender OR transgendered OR transsexual OR transwoman OR transwomen OR transman OR transmen OR "Gender Dysphoria" OR "gender dysphoria" OR “gender affirming”) AND (Hormone OR hormonal OR "Hormone Replacement Therapy” OR endocrine OR Estradiol OR Progesterone OR Testosterone OR spironolactone) AND (fertile OR fertility OR infertile OR infertility OR sterility OR reproductive OR reproduction OR pregnancy OR spermatogenesis OR “sperm count” OR “sperm motility” OR “post-surgical tissue” OR “cumulus-oocyte complexes” OR ovary OR ovaries OR uterus OR testes)

Search 2:

("sex reassignment" OR “sex change” OR "gender change" OR "gender reassignment" OR "cross-gender" OR “cross-sex” OR transgender OR transgendered OR transsexual OR transwoman OR transwomen OR transman OR transmen OR "Gender Dysphoria" OR "gender dysphoria" OR “gender affirming”) AND (Hormone OR hormonal OR "Hormone Replacement Therapy” OR endocrine OR Estradiol OR Progesterone OR Testosterone OR spironolactone) AND (“polycystic ovary”)

Search 3:

("sex reassignment" OR “sex change” OR "gender change" OR "gender reassignment" OR "cross-gender" OR “cross-sex” OR transgender OR transgendered OR transsexual OR transwoman OR transwomen OR transman OR transmen OR "Gender Dysphoria" OR "gender dysphoria" OR “gender affirming”) AND (Hormone OR hormonal OR "Hormone Replacement Therapy” OR endocrine OR Estradiol OR Progesterone OR Testosterone OR spironolactone) AND (“anti-Mullerian hormone”)

Search 4:

("sex reassignment" OR “sex change” OR "gender change" OR "gender reassignment" OR "cross-gender" OR “cross-sex” OR transgender OR transgendered OR transsexual OR transwoman OR transwomen OR transman OR transmen OR "Gender Dysphoria" OR "gender dysphoria" OR “gender affirming”) AND (Hormone OR hormonal OR "Hormone Replacement Therapy” OR endocrine OR Estradiol OR Progesterone OR Testosterone OR spironolactone) AND (“twin study” OR twins)

Search 5:

("sex reassignment" OR “sex change” OR "gender change" OR "gender reassignment" OR "cross-gender" OR “cross-sex” OR transgender OR transgendered OR transsexual OR transwoman OR transwomen OR transman OR transmen OR "Gender Dysphoria" OR "gender dysphoria" OR “gender affirming”) AND (Hormone OR hormonal OR "Hormone Replacement Therapy” OR endocrine OR Estradiol OR Progesterone OR Testosterone OR spironolactone) AND (ovulation OR ovulate OR "LH surge")

Final search:

("sex reassignment" OR “sex change” OR "gender change" OR "gender reassignment" OR "cross-gender" OR “cross-sex” OR transgender OR transgendered OR transsexual OR transwoman OR transwomen OR transman OR transmen OR "Gender Dysphoria" OR "gender dysphoria" OR “gender affirming”) AND (Hormone OR hormonal OR "Hormone Replacement Therapy” OR endocrine OR Estradiol OR Progesterone OR Testosterone OR spironolactone) AND (fertile OR fertility OR infertile OR infertility OR sterility OR reproductive OR reproduction OR pregnancy OR spermatogenesis OR “sperm count” OR “sperm motility” OR “post-surgical tissue” OR “cumulus-oocyte complexes” OR ovary OR ovaries OR uterus OR testes OR “polycystic ovary” OR “anti-Mullerian hormone” OR ovulation OR ovulate OR "LH surge")

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