A Review of Anatomical Presentation and Treatment in True Hermaphroditism

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A Review of Anatomical Presentation and Treatment in True Hermaphroditism

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Dr. Schiml notes that this paper is outstanding because Jodie tracked down relatively hard-to-find primary research and case studies of individuals with true hermaphroditism. This condition is little understood by the lay public but has tremendous implications for how we understand the genetic and hormonal contributors to sex and gender identity. Jodie researched this topic carefully and presented her review in an objective and informative manner.
Abstract
True hermaphroditism is a condition for which much research has yet to be done. This review looks at 11 research studies as well as 3 other review papers on this subject. This intersex condition, in which the person is born with both ovarian and testicular tissue, differs from pseudo hermaphroditism, a condition where the person’s genotype and phenotype are of opposite genders. In true hermaphroditism, the internal and external genitalia, including the phallus, gonads, labio-scrotal folds, and urethral orifice, can present in any number of combinations. The most common gonad is the ovotestis, a gonad made up of both ovarian and testicular tissue. Almost all true hermaphrodites are born with a uterus, a vagina, and functional ovarian tissue, resulting in not only a high chance of fertility, but also a functional female genitourinary system, which is why most modern research favors a female gender assignment. A rare pregnancy using the frozen sperm from a chimeric true hermaphrodite is presented. Cultured frozen sperm found only two slightly motile sperm, demonstrating the extensive fertility challenges faced by male true hermaphrodites. A large study performed in Egypt in 2001 on 314 intersex children reported a mere 5% of the children received a diagnosis prior to age 3 months, illustrating the need for increased education on intersex in certain medical communities.
True hermaphroditism is the rarest of all intersex conditions, and people who fall into this category are born with both ovarian and testicular gonadal tissue. A more recent term used to describe this condition is Ovotesticular Disorder. It can look similar to gonadal dysgenesis, a much more common intersex condition that also presents with dysgenetic gonads, and is characterized by a progressive loss of germ cells, resulting in incomplete development of the gonadal tissue. The conditions can be distinguished histologically. True hermaphroditism is a different condition than pseudo hermaphroditism, which presents with a gonadal and chromosomal make-up of one distinct gender, and the external genitalia of the opposite gender. The causes of pseudo hermaphroditism include congenital adrenal hyperplasia, prenatal exposure to anabolic steroids or progestin, or in the case of the much less common male pseudo hermaphroditism, an autosomal recessive genetic defect. In true hermaphroditism, both types of gonadal tissue are present, and the appearance of the external genitalia can be quite varied. True hermaphroditism is a heterogeneous condition that has many causes, including 1) the division of an unfertilized ovum with a subsequent fertilization of the two haploid ovum followed by a zygotic fusion in early development, 2) a fertilization of one ovum by two sperm followed by a trisomic rescue of one or more of the daughter cells, resulting in a tetragemetic chimera if both genders of zygotes are present, or 3) a mutation in the SRY gene. The paper by Van Niekerk (1976) describes true hermaphroditism as not a single disorder, but as a set of disorders whose characteristics strongly resemble one another in their presentation of both female and male gonadal tissue.

Although it is usually diagnosed at birth, in rare cases the external genitalia and the gonads may appear normal, and the intersex condition may go unnoticed until adolescence when the gender inappropriate gonadal tissue causes such symptoms as amenorrhea in girls, and in boys symptoms such as gynecomastia, cyclic hematuria or blood in their urine, unexplained abdominal pain; or swelling or hernias can present, often leading to the discovery of a uterus, which may be hypoplastic or underdeveloped (Bhansali, Singh, S., Singh, R., Kumar, Khandelwal & Sialy, 1985). These same types of symptoms
usually occur in patients who either did not have their ovotestis excised or the excision was incomplete, leaving gender inappropriate tissue behind and resulting in discordant adolescent gender development (Wiersma, 2001). Patients who go undetected or untreated will always undergo a certain amount of feminization or virilization; 75% of true hermaphrodite males will develop breasts and half will menstruate. A later diagnosis also brings the risk of malignancies, as the testicular portion of the ovotestis will usually become dysgenetic, which is characterized by abnormal development and increased risk of tumors. The risk of ovarian tissue becoming malignant is not known (Bhansali, et al, 1985).

The anatomy of the internal and external genitalia, including the phallus, gonads, labio-scrotal folds, and urethral orifice, can present in any number of combinations. The patient may present with one ovary and one testis, two ovotestis, or a combination of gonadal types. Gonads can be descended or undescended, and the most common type of gonad seen in true hermaphrodites is the ovotestis, which contains both ovarian and testicular tissue. These ovotestis can be bipolar, with a clear demarcation between the two types of tissues, which allows for a partial dissection of the gonad as well as a preservation of the gender appropriate gonadal tissue. Hormonal tests are required in the case of partial dissection to ensure no gender discordant tissue remains. The ovotestis can also be a mixed ovotestis, in which case the two types of tissue are mixed throughout the gonad. This type of ovotestis usually must be fully removed, due to not only gender discordant hormonal activity but also the high risk of malignancy seen in testicular tissue (Wiersma, 2001). In a study on true hermaphroditism performed in 1995, the percentage of bipolar ovotestis was quoted as 80% and reported to contain a usual end-to-end alignment, as well as a clear microscopic demarcation between the two types of tissue, making the partial resection of the ovotestis easier and more likely to be successful. That said, even the testicular tissue that is preserved has a slight risk of malignancy (Kropp, Keating, Moshang, & Duckett, 1995). A paper written in 1984 by Nihoul-Fekete and colleagues (Nihoul-Fekete, Lortat-Jacob, Cachin, & Jossi, 1984) highlights the importance of
preserving gonadal tissue and thus, hormonal function. They make reference to the earlier historical inclination toward removing all ovotestis when treating true hermaphrodite patients, which sometimes resulted in a bilateral castration. This was prior to our increased understanding of the ovotestis and its common end-to-end female/male tissue arrangement, and the decision to remove the entire gonad was due to the increased risk of neoplasm that happens if traces of gender discordant tissue are left behind (Nihoul-Fekete, et al., 1984). Although a histological verification of the type of gonadal tissue present is required, palpation of the gonads (if possible), can give one a strong indication of the type of tissue present. Testicular gonads are softer than the more firm ovarian types, and if a gonad feels soft at one end and firm at the other, this indicates the probable presence of a bipolar ovotestis (Kropp, et al., 1995). The extent to which the gonads are descended is related to the amount of testicular tissue present (Kropp, et al 1995). Because there is an increased risk of malignant changes associated with testicular tissue, it is recommended that all undescended testicular tissue be removed. Ovarian tissue is usually histologically normal (Van Kiekerk, 1976). The overall opinion of most of the articles in this review is that all gender inappropriate tissue should be removed while leaving the maximum amount possible of the gender appropriate tissue in order to facilitate proper hormonal function.

Labio-scrotal folds can present in a number of ways as well, including as bilateral labia with a clitoris giving the impression of a normally appearing female, or they can appear as scrotal, either with bifid scrotal folds or hemi-scrotal folds, or they can be unequal with one side larger than the other (Wiersma, 2004). The appearance of the phallus can vary as well, and it is often the ambiguous appearance of the phallus that alerts adults to a possible intersex condition. This organ can present with clitoromegaly, phallic chordee, hypospadias, or in rare cases, can appear normal. In the study performed in southern Africa by Wiersma (2004), 79 of 85 patients studied had a penis which ranged in size from large to small, but only half of them (n=43) were considered male by their parents. Forty-two of the patients were thought to be female, and five of those patients
possessed both a clitoris and labia. The variable position of the urethral orifice is of some consideration as well and may require surgery in cases where it is not fully functional.

A common finding in true hermaphroditism is the presence of both a uterus and a vagina, as well as functional ovarian tissue, which makes fertility a likely possibility and is the reason most modern researchers on this subject report a higher success rate when patients are assigned and raised female. A study done in 1994 that looked at 22 cases of true hermaphroditism found that a vagina was present in all cases, and a uterus was present in 17 (Hadjiathanasiou, Brauner, Lortat-Jacob, Nivot, Jaubert, Fellous, Nihoul-Fekete, & Rappaport, 1994). A review by Van Kierkerk (1976) which looked at 364 globally documented cases of true hermaphroditism, including 27 they personally reviewed, found that ovulation occurred in 50% of the ovotestis, spermatogenesis was never seen in the testicular portion of the ovotestis, and in normal testis, spermatogenesis was witnessed in a mere 12%.

Although this fascinating condition is the least common type of intersex condition and accounts for less than 10% of all intersex conditions (Krstic, Smoljanic, Vukanic, Varinac, & Janjic, 2000), a curious phenomenon occurs in the black South African population, where a disproportionately high percentage of intersex conditions found there are diagnosed as true hermaphroditism. As a result, much research on this condition is in this part of the world. It is not yet known what factor(s) account for this disproportion. Another puzzling factor in this much misunderstood condition is the development of testicular tissue in the absence of a Y chromosome. In the review by Van Niekerk (1976), 89 of the 340 cases reviewed showed an absence of a Y chromosome. Fifty cases of XX males were also reported. Different theories have emerged as to how this mysterious phenomenon occurs, but none are conclusive.

Once a person has been given the diagnosis of true hermaphroditism, much focus and energy is put into the task of gender assignment by the medical community, and this is usually followed by corrective surgery. This is contrary to the recommendations given by the Intersex Society of North American
(ISNA) which does recommend a gender assignment, as well as medically necessary surgery such as urethral defects, but advocates postponing genital “normalizing” surgeries until the child is mature enough to make informed decisions concerning their own futures. That said, most research done on this condition includes both gender assignment and gender “corrective” surgeries, including specific criteria on which to base the gender designation. Historically, a preference for selecting a male gender was shown by the medical community, but this was prior to our increased understanding of the anatomical and physiological disadvantages male true hermaphrodites can sometimes face. In an analysis of 367 cases of true hermaphrodites going back 75 years, 56% to 75% were raised male (Luks, Hansbrough, Klots, Kottmeier, & Tolete-Veleck, 1988). However, more recent studies illustrate the physiological advantages of being raised female. Those born with true hermaphroditism frequently possess both a vagina and a uterus, giving them a likely chance at fertility as well having a high percentage of functional internal and external organs, making it easier to reconstruct a genitourinary system that functions properly. In direct contrast, those raised male have little or no chance of fertility, their sexual organs are often insufficient, and testicular tissue can degenerate and then become malignant (Luks, et al, 1988). In their article, Luks and colleagues found that almost 80% of the cases had adequate female sexual and reproductive organs, allowing for both fertility and sexual function. Conversely, only a small number of them had adequate external genitalia needed for male sexual function. Luks and colleagues maintain that gender assignment can be based solely on the appearance of the external genitalia. This assertion is based on their review of 528 previously documented global cases of true hermaphroditism, including their own, in which they observed a correlation in 114 of those cases between the appearance of the external genitalia and the karyotype, age of diagnosis, laparoscopic findings, the sex of rearing. They believe that these factors specifically reflect the psychosexual capacity of the child. In their opinion, compatibility between internal and external organs either already exists or can be accomplished through reconstructive surgery.
This belief led them to devise a system of classification for external genitalia:

**Class I: female genitalia.**
Normal or mildly enlarged clitoris.

**Class II: labioscrotal folds not fused.**
Enlarged clitoris, female urethra and separate vaginal ostium, labia minora are present or absent. Gonad(s) may be palpable in labioscrotal folds.

**Class III: labioscrotal folds partially fused.**
Probable posterior fusion, present phallus with chordee, penoscrotal (third degree), or perineal (fourth degree) hypospadias; vaginal ostium is present or absent. Gonads may be palpable in labioscrotal folds.

**Class IV: labioscrotal folds fused.**
No distinct scrotal sac; phallus with cordee and penoscrotal (third degree) hypospadias. Vaginal ostium present or absent. Gonads may be palpable in labioscrotal folds.

**Class V: Scrotal sac.**
Sac may be hypo-plastic, penis short or normal, chordee present or absent. Penile (second degree) or penoscrotal (third degree) hypospadias with no vaginal ostium. Gonad(s) may not be palpable in scrotum.

**Class VI: male genitalia.**
Normal or small penis, chordee may be present, as well as normal urethra or coronal (first degree) hypospadias. Gonad(s) may not be palpable in scrotum.

Class I through IV should be raised female, and class V and VI should be raised male.

In keeping with most of the other researchers on this topic, Luks and colleagues advocate for prompt gender assignment upon diagnosis, and this system was meant to assist in this goal. Of the
eight true hermaphrodites included in their study, six were raised as girls and two as boys. One child was referred to them at age 11; she had already been raised male despite the appearance of his external genitalia, which otherwise would have given him a female assignment. According to their paper, he had already identified as male, so they performed the male reconstructive surgery. Perhaps a few more years of development should have been considered before doing surgery, allowing him the time and maturity required to make an emotionally and mentally informed decision.

A study performed in France and published in 1994 (Hadjiantanasiou, Brauner, Lortat-Jacob, Nivot, Jaubert, Fellous, Nihoul-Fekete & Rappaport, 1994) based gender assignment on the patient’s age, presence of a uterus, extent of virilization of the external genitalia, and the ability of the testicular tissue to secrete testosterone after hCG stimulation. Their results also demonstrate a higher success rate when true hermaphrodites are raised female. They report that most of their patients had both a uterus and a vagina as well as normal ovarian tissue. Given this anatomical make-up, the reconstructive surgery is easier and more successful, and the patients are left with functional female anatomy. Eight of them had successful pregnancies. Patients without a uterus who demonstrate a high level of virilization should be raised male (Hadjiantanasiou, et al., 1994).

The study by Barren and associates (1980) assert that one’s gender identity is firmly entrenched by age two-and-one-half and any diagnosis made after this age, as well as any surgical, hormonal or other treatment, should retain the original established gender. Diagnoses made before that age should base gender assignment on the potential functionality of the urogenital system. Future fertility and chromosomal results are important, but less so than the patient’s potential urogenital function (Braren, Slonim, Warner, O’Neill, Burr, & Rhamy, 1980). They recommend that patients assigned as female undergo reconstruction of their external genitalia prior to age three, in contrast to other non-cited research quoted in this paper that recommends waiting until either puberty or marriage. A non-sexist and more modern and useful approach to this recommendation, which was quoted in 1980, would perhaps include a recommendation
of surgery prior to consensual sexual activity, as opposed to surgery prior to marriage. A partial clitorectomy or recession is also advocated before age two, as well as a removal of all contrary internal organs and testicular tissue, and a complete removal of any ovotestis during the exploratory laparotomy. This recommendation to remove the entire ovotestis differs from most researchers reviewed in this paper, who seem to favor a partial dissection of ovotestis, with a maximum amount of preservation of gender-appropriate gonadal tissue in order to assist future hormonal function. No reason was given for this recommendation. Although Braren and colleagues agree with other researchers that a female gender assignment generally has better outcomes, they also developed criteria for which a male gender should be assigned:

1) children whose diagnosis happens later and who already identify as male
2) children with a well-developed phallus regardless of age
3) and children whose parents feel strongly that they be raised male.

Once a male gender assignment is made, staged pseudovaginal hypospadiac surgeries should be completed prior to age four, and testicular prosthetic placement should be done after the onset of puberty (Braren, et al., 1980). (Notice the subject of marriage was not included in this recommendation.)

In 2001, a substantial study on 314 intersex children, including 18 true hermaphrodites, was performed in Egypt, which illustrates the strong cultural influences that can affect not only gender assignment and views on intersex, but also the level of awareness in the medical community. The statistics concerning age of diagnosis highlight a remarkable lack of awareness of intersex conditions in this particular medical population. Of these 314 children, a scant 5% (n=16) received a diagnosis before the age of 3 months, and most of those patients presented with medical conditions such as salt-losing 21-hydroxylase deficiency. Forty-nine cases were diagnosed during or after onset of adolescence, and 20 of those cases received initial medical attention because of virilization from undiagnosed 5
a-reductase deficiency or PAIS (Dessouky, 2001). Religious views in this country weigh heavily on the subject of intersex, and the “Fatwa” (the recognized authority on Islamic law) dictate that gender assignment be based on what anatomy is predominant, and it is required that any contradictory tissue be removed in order to avoid future corruption. Once diagnosed, this study utilized the Prader scale to assess the degree of genital masculinization and virilization, and the children were placed in one of two categories:

1) those whose genotype did not match with their gender of rearing were labeled as “sex misassigned,” which made up 31% of the patients
2) those children whose sex of rearing was discordant with their anatomy were labeled as having “discordant sex,” which made up the remaining 69%.

The majority of the true hermaphrodites in this study presented with masculinized external genitalia (grade III, IV, and V). One child, already being raised male, was grade II but had an enlarged clitoris, and his male gender was retained, despite the fact that his diagnosis using the Prader scale would have given him a female gender assignment. Gender assignment in this study stressed the functional capacity of the external genitalia most importantly, although perhaps for different reasons than the study by Luks and colleagues, and their rates of female-to-male ratios of gender assignment are quite different. All of the true hermaphrodites in the study by Dessouky (2001) were raised male save one, a patient who had a non-identical normal male twin, and this patient was reassigned female at the age of one-and-a-half. (The presence of a male twin underscores this gender change to female.) The percentage of patients raised male in this study is in stark contrast to the numbers presented in other research papers reviewed here. Male assignment is given in all cases where even an inadequate phallus is present, despite gonadal make-up. Patients who possess both an adequate phallus and a vagina are given an exploratory laparotomy to look for the presence of a normal testis, and if one is found then a male gender is assigned. Of the 18 cases of true hermaphrodites in this intersex study, 94% (n=17)
possessed a male phenotype. The decision to maintain the male gender in 17 of them was made in spite of the fact that 10 of these patients had both Mullerian duct organs and a normal ovary, and the related high chance of fertility. This may have been due not only to the age of diagnosis and subsequent virilization of the external genitalia, but also to parental pressure and perhaps even the increased freedom afforded to males in this strict gender dichotomous society. In Egypt, as well as some other Muslim countries, males inherit twice the amount as females from deceased family members. They have freedom to travel and circulate whereas women are much more restricted. In addition, in some communities, male witness carries twice the value as female. Given these male entitlements, it is easy to see why male gender assignment might be preferred. The author of this study vigorously emphasized that much attention was given to the parents concerning gender assignment; they were firmly reassured that the medical attention would result in a definite gender assignment, and there was no possibility of any “in-between” gender being assigned to their child. This particular culture does not currently allow for any intersex state and has strong cultural and religious dictates and requirements concerning gender assignments. All medical staff were advised to refrain from voicing opinions concerning particular patients’ gender until decisions were made. Once the gender is assigned, virtually all patients undergo reconstructive surgery including excision of all gender-discordant tissue. Those patients assigned a male gender initially undergo a correction of any urethral defects as well as any scrotal abnormalities and have their uterus and contradictory gonads removed. Later surgeries are performed as well, in order to correct any undescended testes and remove all breast tissue. As of the writing of this article in 2001, this particular medical community does not agree on the optimal age for female reconstruction. All agree on an initial treatment of clitoral enlargement, but some members of the medical community advocate postponing vaginoplasty (a reconstructive surgery to reconstruct a vaginal canal) until puberty, while others advocate performing both surgeries either the first week of life or upon diagnosis. The present study favored the later. In the early part
of the study, if severe virilization and clitoromegaly was observed, treatment included total clitorectomy and simple introitoplasty (a surgical procedure to correct urogenital sinus malformations). Further into the study, they adopted the recommendation that neurovascular supply to the glans be maintained during surgery in order to increase sexual function. After completion of the study, 43 intersex patients subsequently changed their gender, 31 to male and 12 to female. Forty-one patients who fell into the “discordant sex” category continued in the gender they had been raised in, despite anatomical and functional challenges that would have been minimized had they chosen the opposite gender. Most of them were raised male (n=30) (Dessouky, 2001).

A long term, 40-year study was done on 33 patients with true hermaphroditism who were treated between 1965 and 2005. This study emphasized gonadal function before and after undergoing conservative gonadal surgery (Verkauskas, Jaubert, Lortat-Jacob, Thibaud, & Nihoul-Fekete, 2007). Conservative gonadal surgery is described as the partial resection of ovotestis with the preservation of the maximum amount possible of gender-concordant tissue, while resecting all gender discordant tissue. This type of gonadal surgery remained consistent throughout the study. The average length of time the patients were followed is 11 years. 73% of the patients were diagnosed prior to the age of 6 months, and 21 were raised female and 12 as male. This study reported that 88% of the ovotestis presented in an end-to-end fashion, with a clear division between the two types of tissue, which allows for easier partial dissection. Spermatogenesis was not witnessed in any of the cases, and 73% had a uterus. It was also observed that over time the testicular tissue usually became sclerotic and abnormal, losing germ cells and never developing fully. However, the ovarian tissue usually maintained its functionality. No post adolescence gonadal tumors were seen. Three of the patients’ ovotestis were misdiagnosed as normal gonads and were subsequently left whole when they should have been partially dissected, leaving gender-discordant tissue and resulting in hirsutism (excessive facial or chest hair) in one female patient and cyclic testicular pain in two male patients. The study also reported a
common mistake of excising the wrong parts of the gonads. Spontaneous puberty was witnessed in nine patients between the ages of 11 and 14. One male patient entered puberty at age 17. Four of the patients did not have their age of pubertal onset documented. An absence of puberty was seen in one 13-year-old boy, and four patients had to be hormonally induced after undergoing bilateral castration. Low testosterone and a subsequent decrease in virilization were seen in two males who required testosterone replacement.

Amenorrhea was documented in two post-pubertal girls, both of whom presented with a hemi-uterus during exploratory surgery performed when they were children, and one of whom had no vaginal communication. Two of the female patients who did not menstruate presented either with a dystrophic or aplastic uterus. Four female patients had normal cycles, two had dysmenorrhea or oligomenorrhea, and two patients who received a bilateral gonadectomy were subsequently treated with hormones and then had normal cycles. No cases of fertility were seen, and analysis of sperm consistently showed azoospermia. Of the 9 patients who gave information concerning sexual activity, 4 men reported sexual satisfaction. One of these men was married and was considering the possibility of medically assisted fertilization. One 18-year-old male, who had had bilateral resection of the ovotestis at age 7, was unable to achieve erections and was given androgen substitution. Of the 4 women who reported on sexual satisfaction, only 1 was engaging in regular intercourse. She had 1 normal ovary. Three women aged 23 to 36 reported that they had never had sexual relations. Two of them had had a bilateral gonadectomy, and 1 maintained only half of her ovotestis. The complaints heard most often from these patients were complaints of vaginal stenosis, amenorrhea, hot flashes, recurrent cystitis, and psychological problems. No cases of gender dysphoria were reported (Verkauskas, et al., 2006).

Many of the articles reviewed here report a lack of male true hermaphrodite fertility. However, in 2004 in Japan, a successful pregnancy and delivery from a chimeric infertile 46 XX,XY karyotype male utilizing intra-cytoplasmic sperm injection from his frozen testicular sperm was reported (Sugawara, Tokunaga, Maeda, Komaba,
& Araki, 2004). During the procedure, in which the frozen sperm were thawed and cultured, two moderately motile sperm were seen, with only one having normal membrane morphology. The baby, delivered at normal gestation in September of 2003, was a normal 46XX female.

The study of true hermaphroditism increases not only our knowledge of this fascinating and enigmatic condition but leads also to a greater understanding of sexual dimorphism in all human beings and perhaps even a greater understanding of our humanity.

References


