The Ethics of Fertility Preservation for Pediatric Patients With Differences (Disorders) of Sex Development

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Differences (disorders) of sex development are diverse conditions with variations in chromosomal, gonadal, and/or genital development. Fertility potential in this population is variable. Recent investigations into fertility potential in those previously thought to be infertile suggest that the majority may have fertility potential through experimental protocols. Fertility preservation may be more successful if pursued in childhood. As fertility research and techniques advance, it is important to carefully consider pediatric ethical issues specific to this population, including gonadectomy, consent/assent, experimental treatment and false hope, cost and insurance coverage, genetic transmission to offspring, and gender dysphoria.

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Care for individuals with differences (disorders) of sex development (DSD) has changed substantially over the last decade, spurred by the 2006 International Consensus Conference on intersex disorders [1]. A 2016 global update addressed continuing controversies and changes in perception and approach to diagnosis and care [2]. Fertility-related care in this field is in its infancy. Individuals with DSD face the possibility of infertility due to inherent subfertility from abnormal gonadal development or progressive gonadal failure, prophylactic gonadectomy (PG), and anatomic barriers. There are many questions about fertility potential in individuals with specific DSD. Early research, however, indicates that individuals with DSD who were previously assumed to be infertile may have biological fertility potential [3].

The field of oncofertility was founded to bridge the gap between oncology and reproductive science to offer and improve fertility options for cancer survivors [4]. As the field of oncofertility has grown, its focus has broadened to foster collaboration and progress for other populations facing infertility. Thus, individuals with DSD may also benefit from advancing techniques for fertility preservation (FP), such as cryopreservation of mature or immature...
gonadal tissue [5]. In all populations, there are important ethical considerations surrounding reproductive decisions, but there are unique issues in DSD that must be addressed. These include PG, balancing optimal timing of FP with benefits of retaining gonads, assertions of human rights organizations regarding pediatric assent and consent, and preservation of gametes that do not match gender identity. We sought to initiate this ethical exploration.

1. Ethics of Gonadectomy

A. General

Gonadectomy is performed in some patients with DSD who are at increased risk for germ cell cancer (GCC) [2]. The clinical perception has long been that such gonads, without usual hormone function and fertility potential, lack purpose and that, given the GCC risk, should be removed. However, understanding of malignancy risk is expanding such that GCC risk can be stratified by specific DSD diagnosis. Some conditions confer low risk [e.g., risk in complete androgen insensitivity syndrome (CAIS) is <5%, whereas others confer intermediate or high risk [e.g., partial AIS with cryptorchidism risk is ~50%] [6]. Accordingly, this risk stratification has allowed for timing of gonadectomy recommendations to be more individualized based on specific diagnoses. For example, van der Zwan and colleagues recommend postpubertal gonadectomy or observation for patients with CAIS and strong consideration of prepubertal gonadectomy for those with partial androgen insensitivity syndrome [7]. GCC may take years to become invasive malignancy, which is generally localized and highly curable; thus, observation protocols may be reasonable for select individuals [8].

Controversy surrounding PG, however, is also increasing. Some argue that gonadectomy results in a physical and emotional loss for patients. Some patients with DSD report a reduced sense of well-being with postgonadectomy hormone replacement therapy compared with endogenous hormones [9, 10], and PG was associated with suicidality in one recent paper [11].

In a more holistic sense, some view PG as damaging to one’s sense of self as a woman or man. Even though a woman’s ovaries are not visible, many women place “great symbolic value on ovaries ... as the source of female normality” [12]. Indeed, some women consider their ovaries a necessary part of their feminine identity and as something that makes them “whole” [13]. Although seemingly counterintuitive given discordance of testes and female gender identity, intersex women’s loss of testes may resemble nonintersex women’s loss of ovaries.

Some intersex women regard noncancerous gonads as necessary to their feminine identity, a source of feminizing hormones and potential gametes. Many men also view their reproductive organs as essential to their gender and sexual identity [11, 14], with loss challenging masculinity.

B. Human Rights Considerations

In addition to the above considerations about gonadectomy, DSD surgery in general is increasingly controversial. The United Nations and World Health Organization called for cessation of all medically unnecessary intersex surgery before age of majority, finding it a violation of children’s human rights to bodily autonomy [15–17]. Further discussion of age of consent and assent is detailed below. With PG, distinguishing “necessary” vs “unnecessary” is challenging as knowledge about future fertility and GCC risk evolves.

C. Technical/Surgical

PG surgery has risks of anesthesia, blood loss, and infection. Although these risks are low for PG and gonadal biopsy procedures relevant to FP [18, 19], the US Food and Drug Administration recently issued a warning that “repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years ... may affect the development of children’s brains” [20], and experts have recommended avoiding
nonurgent procedures requiring general anesthesia in this age group. For those at low risk who can consent and accept uncertainty associated with observation, surgical risks and ethical concerns may outweigh perceived benefits of PG.

D. Fertility Potential

As previously stated, infertility has often been assumed in many DSD diagnoses, substantiating beliefs that gonads “lacked purpose.” Increasingly, assisted reproductive techniques have allowed some individuals with DSD to carry pregnancies or to harvest sperm [21]. Expanding upon traditional views of fertility, preliminary evidence suggests emerging technologies may enable even greater biological fertility [3, 5]. Finlayson et al. reported in a pilot study that 68% of individuals with DSD had germ cells present, with more likely to be present at younger ages. If future studies confirm these findings, and emerging technologies are able to be translated into live births, the assumption that gonads of many patients “lack purpose” may need reconsideration.

E. Timing

As we acquire data about fertility potential in DSD, this challenges us to reassess the timing of gonadectomy, taking into account optimization of FP. In a small population, it has been shown that germ cell counts decline with age, suggesting that successful preservation of fertility potential may be best achieved at younger ages [3]. Thus, if gonadectomy is delayed until the age of majority in a patient with GCC risk, there may also be a lower likelihood of gametes or germ cells to preserve. This leads to a question of whether a reasonable approach might be to partially or completely remove one gonad for FP at young age, while leaving the rest of the gonadal tissue in place to facilitate potential endogenous hormonal function, holistic sense of self, and autonomous decision making. If such an approach was taken, at what age should FP be performed, considering the risks of pediatric anesthesia? Additionally, FP for very small gonads may necessitate gonadectomy rather than gonadal biopsy, and complete gonadal removal may be more likely if FP is attempted at very young ages.

2. Consent and Assent

An ethical issue in all pediatric practice is children’s ability to provide assent and consent for medical treatment. Although parents are generally proxy decision makers, considering their child’s best interest and values, reproductive decisions are seen as more personal than other health care decisions [13]. It may be difficult for parents to distinguish their own best interests from those of their children [5]; therefore, reproductive decisions are best made by individuals for themselves. However, this may be impossible in DSD care, when FP or fertility-compromising treatments are proposed for children under the age of majority. A child’s greatest likelihood of successful FP may be as a minor. When treatments for DSD and/or decisions about FP are made before children have legal decision-making rights, parents and children may later disagree regarding choices that were made. If children cannot legally consent, they should be included in the decision-making process and give assent if possible [18, 19]. However, even with assent, decisional regret may occur because young patients cannot always predict their future wishes [22].

3. Experimental Treatment and False Hope

Decisions regarding FP in DSD are complicated by the unknown inherent fertility potential associated with some DSD conditions, and the possibility of experimental FP techniques being applicable to this group. Because maturation of immature germ cells to mature eggs and sperm occurs at puberty, some postpubertal individuals with DSD could benefit from established FP methods. In contrast, prepubertal patients only have the option for experimental gonadal tissue cryopreservation [5], which relies on the development of technologies to
mature germ cells in vitro. These technologies are rapidly advancing so that experimental treatments on cryopreserved tissue may be successful in the future [23]. There is concern that uncertain success and potential surgical and psychological risks do not justify experimental treatment given that children are a vulnerable population. Rather than prohibiting FP broadly in pediatric populations, McDougall argues that this decision should be left to parents because they are best suited to make value judgments regarding risk/benefit analysis [24]. Although choosing an FP option that requires gonad removal may infringe on the rights of children with DSD to bodily autonomy, forgoing FP may have a psychological risk of adult children thinking their parents did not uphold their reproductive autonomy [24].

A general concern with experimental treatments, including pediatric FP, is that they can lead to false hope, “a type of psychological risk that occurs when patients are misled about the possibility of success for a particular treatment” [25]. False hope exists even for established treatments, but can be more pronounced for experimental treatments with greater uncertainty regarding likelihood and degree of success and potential risks. In the case of DSD, false hope regarding FP could cause patients, parents, or providers to proceed with complete or partial gonadectomy that they might later regret.

4. Cost and Insurance Coverage

FP is expensive (ranging from thousands to tens of thousands of dollars) and requires storage of frozen gametes [26]. Insurance companies rarely cover FP, even for cancer patients [27, 28], and FP for “delayed” childbearing is mostly considered elective. In the oncofertility context, some argue that FP should be covered to treat iatrogenic infertility because treatment of other iatrogenic conditions is covered [27]. A similar argument can be made for reproductive rights in DSD: FP should be covered because the treatment of DSD (e.g., gonadectomy) can engender infertility. For certain types of DSD, it is not the treatment, but rather the condition itself, that leads to infertility (e.g., Turner syndrome). There are some parallels to coverage of assisted reproductive technology (ART) for adults with infertility that is considered a medical condition, which will only be strengthened if prepubertal FP becomes standard of care.

Unlike infertility patients, but similar to pediatric oncofertility patients, DSD patients use ART not to have children now, but to preserve future fertility. As such, some object to coverage of FP as “elective,” but this misses its potential psychosocial benefits; infertility can result in serious psychological distress [29]. Oncofertility studies show that FP is a source of “frozen hope” and optimism that can improve overall well-being [30]. Today, much of medicine focuses on quality of life, not just life-saving treatments. In fact, ART is increasingly seen as standard medical care in the United States; 14 states in the United States now have insurance mandates requiring coverage of ART for infertility patients [28]. Others object to FP because of expense. On an individual basis, ARTs are costly. They seem less so when viewed at the societal level, currently comprising just 0.06% of total U.S. health care expenditures [31]. Excluding FP from insurance coverage raises distributive justice concerns that only children from middle- or upper-class families will have access.

5. Transmitting Genetic Condition to Offspring

Because many DSD are heritable genetic conditions, there is concern about transmission to offspring. DSD are rarely associated with serious medical conditions, such as Denys-Drash syndrome, with a high risk of renal failure and Wilms tumor. Some ethicists argue that individuals have an obligation to produce the “best” children they can, and that it is immoral, or at least irresponsible, to knowingly have children who will have a medical condition or disability [32]. Disability scholars and intersex advocates challenge this eugenic viewpoint, asserting that people with disabilities can lead happy, productive lives [33]. Many who live with DSD object to the language of disorder and disease [34]. For adults concerned about having children like themselves, preimplantation genetic diagnosis can screen embryos for genetic differences.
6. Parental and Provider Pressure and Reluctance

The frequent concern in pediatric oncofertility that children will feel pressured to undergo FP and obliged to pursue future fertility [35] also applies in DSD. Recognizing the effort and expense of FP, children could feel obligated to use frozen materials. Yet parents allocate time and money toward many possible options that may benefit their children (e.g., pretax dollars toward college savings) that children can choose to use or not. By creating more choices, parents are giving their children an open future, thereby enhancing future autonomy [36].

Social norms can compound pressure to pursue FP, especially those that imply motherhood is a necessary component of womanhood [37]. Because children may assume when providers present FP that it is a requirement rather than a choice, developmentally appropriate conversations with pediatric patients are crucial to elucidate and address concerns children themselves may have [38].

The opposite of provider pressure is provider reluctance to offer FP. Historically, and on an ongoing basis, multiple barriers to offering FP to cancer patients include lack of awareness, physician perception that FP will delay cancer treatment, and that certain patients cannot afford it [39, 40]. We have anecdotally observed similar reluctance in providers caring for patients with DSD.

7. Gender Identity and Gender Dysphoria

DSD conditions are sometimes associated with gender nonconformity in early childhood. In the majority of cases, gender nonconformity is not associated with gender dysphoria (GD), defined as distress stemming from incongruence between early sex assignment and subsequent gender identity [41]. Rates of GD, however, are higher in DSD conditions than in the general population, with specific rates varying as a function of initial gender assignment, specific diagnoses, and their varying manifestations [42–44]. Among the subset of youth with DSD and GD, body dysphoria associated with GD may limit compliance with physical processes required for FP [41]. For instance, cryopreservation of ejaculated sperm through masturbation is considered the “simplest and most reliable method” of FP for birth-assigned males because it is medically noninvasive [45]. Masturbation can be challenging for many adolescents for physical or psychological reasons [37], particularly so for youth initially assigned male but identifying as female. If youth are unable to provide a sperm sample via masturbation, testicular sperm extraction may be used. Unlike masturbation, this surgical procedure carries some physical risks, with related emotional distress [37]. FP can have similar physical and emotional difficulties for birth-assigned females identifying as male [46]. Oocyte cryopreservation requires ovarian hyperstimulation and transvaginal oocyte retrieval, which may be particularly traumatizing for those with body dysphoria. In both groups, high-dose estrogen or testosterone required for FP can create or exacerbate body dysphoria because of resultant irreversible physical changes inconsistent with gender identity.

With or without co-occurring GD, discordance between gametes and gender identity is common in DSD. For example, in CAIS, affected individuals almost always identify as female [47], but their gonads are testes with potential sperm. In our experience with peer support groups, these women are not generally concerned about using gametes discordant with gender identity. Anecdotally, providers express concern that it could be psychologically difficult and cause hesitation in utilizing preserved gametes, as for some transgender women, for whom the existence of stored semen samples is a reminder of a “male past” that causes them to feel like “not a complete woman” [48, 49]. Discordance between gametes and gender identity may also affect ability to reproduce with a future partner depending on sexual orientation. For example, a heterosexual woman with CAIS would not be able to use her preserved sperm with the sperm of a future male partner to produce offspring genetically related to both of them.
8. Conclusion

Research is needed to advance fertility options for individuals with DSD, including scientific and medical investigation of questions about fertility potential, attitudes toward fertility, decision-making processes, and surgical techniques. As we establish this new field, we must also be responsible in our ethical interrogation, carefully considering issues discussed here, including gonadectomy, autonomy in reproductive decisions, cost, false hope, provider reluctance, and GD.

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