Ethics, gonadectomy and risk of parental choices

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Abstract

This case relates to an infant with Turner syndrome harboring the Y chromosome(TS+Y) and explores the boundaries of parental decision-making.

Traditionally, gonads have been surgically removed in early childhood in this condition because of the risk of gonadoblastoma and potential malignant transformation. However, in the case, the infant's parents do not wish for surgery. In other congenital variations of sex characteristics (i.e., differences/disorders of sex development, also termed intersex traits), some institutions report a shift in the last decade away from early surgical management for some conditions, in favor of allowing more children to be involved in decision making when they are old enough to participate meaningfully.
But should that approach change when there is a risk of malignancy?

Three commentaries are presented. One outlines the evidence (or lack thereof) around the management of TS+Y, including the possibility of endocrine function and spontaneous puberty initiation from gonads left in situ, as well as the risk of gonadoblastoma and malignant transformation. A second commentary outlines ethical considerations around early surgery in intersex conditions, highlighting implications for the child's bodily integrity and future bodily and sexual autonomy. The third commentary analyses the case in terms of pediatric ethics, medical uncertainty, and the zone of parental discretion.

Though specifically concerning the condition of TS +Y, this discussion provides a framework to consider the ethical boundaries of parental decision-making when it comes to genital surgery in persons more generally who have congenital variations of sex characteristics (VSC).

Case

K is a 2 year old girl who was born at 38 weeks gestation via normal vaginal delivery with a birth weight of 3047g. Antenatally, she was found to have cystic hygroma and fetal echocardiography at 24 weeks showed a perimembranous ventricular septal defect (VSD), aortic coarctation, mildly hypoplastic aortic arch and mildly hypoplastic left ventricle. She had previously undergone non-invasive prenatal testing (NIPT) which showed low risk for aneuploidy, 22q11 deletion and other deletion syndromes. It is well known that NIPT is unreliable in detecting mosaicism or single gene disorders.

Examination after birth revealed some dysmorphic features suggestive of Turner syndrome. K had female-typical genitalia and there was no signs of virilization clinically. There was a cardiac murmur due to her cardiac condition. A karyotype was performed for her which showed 45X(10)/46XY(10) mosaicism. Ten metaphases out of twenty showed loss of the Y chromosome. She had markedly elevated FSH 30.8 Iu/L but normal LH 0.3 IU/L and testosterone levels of 0.21nmol/L.

Risk of gonadoblastoma and malignant transformation was communicated to K's parents and a gonadectomy was recommended. Initially the parents wanted to focus on the coarctation surgery and did not wish to perform the gonadectomy in the same general anaesthesia setting. They argued that without the heart defect, a karyotype may not have been done and the Y chromosome would not have been picked up till K was much older. K underwent a coarctation repair at 2.5 months of age and the recovery was uneventful.

Subsequently K's parents decided, against medical advice, that they wished to preserve K's gonads. They were aware of recommendations to delay surgery in cases with differences of sex development. They also remained hopeful that the gonads may be able to produce sex hormones allowing for natural puberty to occur rather than K being dependent on hormone replacement for pubertal induction. They were aware that if the gonads are non-functioning, K will still require pubertal induction using oral or transdermal female hormones.

To manage the risk of malignancy, regular ultrasound surveillance was arranged for K and the scans did not reveal an tumour suggestive of gonadoblastoma thus far. K's parents were given the option of gonadal biopsy with laparoscopy to further assess the risk of malignancy and help to inform their decision making but they were not keen to pursue it.

Commentaries

Dr Cindy Ho, Paediatric endocrinologist

Turner syndrome (TS) is a chromosomal disorder that affects females who have one intact X chromosome and complete or partial absence of the second sex chromosome.
Most patients have characteristic facial appearance, short stature and ovarian insufficiency, with some having distinctive congenital cardiovascular, renal, skeletal and digital anomalies. There is also a constellation of medical conditions more commonly seen in patients with TS. Those with 45X/46XX mosaicism typically have a milder phenotype. Phenotypic males with 45X/46XY (or other variants) are excluded from the diagnosis of TS and are more commonly labelled as having mixed gonadal dysgenesis.
Some patients with TS also have genetic material from the Y chromosome ("TS+Y") but are phenotypically female like the case we described.

Girls with TS+Y constitute a unique category of TS because of their risk of gonadoblastoma, a premalignant germ cell tumor with risk of malignant transformation.

Reported rates of gonadoblastoma range widely from 2% to 50% and reported rates of malignant transformation are low, from 1% to 12%. Although gonadoblastoma has been identified in infancy, malignant transformation does not typically occur until the second decade of life.[1] There is one report in a girl with 45X/46XY mosaicism who had gonadoblastoma as early as 6 years of age.[2]

Given this risk of malignancy, most paediatric endocrinologists managing such patients will advocate for surgical removal of gonads as early as possible. This is included in the influential international clinical practice guidelines for the care of girls and women with Turner syndrome published in 2017 by Gravholt et al., albeit, the quality of evidence behind the recommendation is rated as low.[3]

Accordingly, this request from parents created an ethical dilemma for my colleagues and me as we have been taught that having a gonadectomy would unquestionably be in the child's best interest. The historic understanding had been that the gonads in children with TS+Y are likely non-functioning and yet pose a risk of malignancy. In that case, leaving the gonads would be of no functional benefit to the child, but would carry a serious (and potentially life-threatening risk).

Following the parents' request, I reviewed the literature for the potential of gonadal function and found a retrospective multi-center cohort that reported that 42% of girls with TS+Y entered puberty spontaneously and 11% had spontaneous menarche, supportive of gonadal function.[1] But there is no way of identifying in advance whether K will fall in to the group that will have gonadal function.

Should I then respect or oppose the parents' decision? The risk of potential malignancy appears serious, but given that most children with this condition have had their gonadal tissue removed it is challenging to quantify the probability of this occurring in children who have the gonads left intact and grow into adulthood.

In other children with intersex conditions, endocrinologists are increasingly supportive of a conservative approach, delaying surgery. But in conditions like this, will support for parental choice and children's developing/future autonomy lead to a future tsunami of gonadoblastoma as these children age? Perhaps only time will tell.

Dr Brian D. Earp, Dr Cynthia Kraus, and Dr Morgan Carpenter

Some procedures on infants and children with congenital variations of sex characteristics (VSC) are ethically contentious, particularly where the intervention is not medically necessary[4] and could be delayed until the child has capacity to decide. When it comes to people's genitalia and preserving their (future) sexual and reproductive autonomy, children's, intersex, and human rights organisations seek to distinguish between "early" (i.e., non-voluntary) interventions necessary for physical health and well-being (often not directly related to the VSC itself) from those undertaken for cosmetic or psychosocial reasons with the aim of "normalizing" genital appearance or function.[5] The aim is to defer surgery where possible until the child is old enough to make an informed decision.

The risk of malignant gonadal tumors developing in certain cases such as Turner syndrome with Y chromosome material (TS+Y) is sometimes presented as a physical health justification for early gonadectomy, as in the case of K. However, relevant data remain scarce and provide an inadequate basis for accurate risk assessment. Moreover, it is the very prevalence of early

gonadectomies that contributes to this scarcity of data. According to a multi-site study of children with VSC undergoing biopsies or gonadectomies between 2000 and 2022: "Estimating the true prevalence [of malignancy in] this population remains challenging due to the historic rate of prophylactic gonadectomy at a very young age."[6 (p.399.e7)]

Meanwhile, improved data availability in relation to other XY traits suggest a historical tendency toward risk over-estimation (discussed below), calling into question reliance on existing data to justify non-voluntary gonadectomies.

Inadequate data combined with a bias toward pre-emptive surgery is a longstanding issue in this area. Since the 1950s, early surgical management even of physically benign VSC traits became standard practice notwithstanding a lack of evidence-based tests of harm versus benefit compared to more conservative approaches.[5] Despite the current default having thus been set without evidence, clinicians have argued since the 1990s, in response to pushback from intersex rights advocates, that clear evidence of *harm* would be required to change the status quo.[7] However, this reverses the burden of proof. It is a truism both of surgical and sexual ethics that non-intervention into a person's genital, sexual, or reproductive anatomy should be the default position unless they have given their consent or there is compelling evidence of medical necessity.[8]

The history of evidence regarding malignancy risk is troubling. A 2006 clinical consensus statement outlined known gonadal tumor rates for a range of traits,[9] describing TS+Y as "intermediate" risk, alongside 17-beta hydroxysteroid dehydrogenase 3 deficiency (17βHSD3),

scrotal gonadal dysgenesis (Y+). Complete androgen insensitivity (CAIS) was identified as low risk but the partial form (PAIS) and intra-abdominal gonadal dysgenesis (Y+) were identified as high risk.

Since then, risk levels associated with gonadal dysgenesis (Y+) are still understood to be high.[10] However, gonadectomies in 17βHSD3 are now associated with sex/gender assignment, not risk of tumors,[11] while tumor risk in (P)AIS is now thought to have been exaggerated.[10] Additional evidence that early gonadectomies are still routine practice for 17βHSD3 and both types of AIS can be found in the few rare instances where medical teams report more openly about such surgeries.[e.g.,12] A commonly-seen interpolation of other factors – such as perceived risk of stigmatization or gender dysphoria – has been described by a committee of the Australian parliament as undermining "confidence in the neutrality of those advocating for surgical interventions."[13, p.88]

This historical context, including the diversity of rationales given for gonadectomies that are unrelated to malignancy risk, provide, in our view, a rational basis for the parents' decision to defer surgery in the hope that their child will be able to experience puberty without exogenous hormones. Such hope for gonadal function is not unrealistic if one considers that, in 2020, the first retrospective multicenter study on this issue reported that among a cohort of children diagnosed after the age of 13 with TS+Y, 42% had evidence of having started to undergo puberty and 11% had spontaneous menarche [1] whereas "early" bilateral gonadectomy is certain to prevent spontaneous puberty and menarche.

In relation to TS+Y, the evidence base for gonadectomy remains inadequate to decide clearly on the basis of medical necessity. In 2023, a multicenter study on TS+Y reported on 16 patients.[6] All had bilateral gonadectomies and histology reports identified evidence of germ cell neoplasia in situ in 3 cases, and none with germ cell tumors. Their risk level was classified as high/intermediate.

In the same year, a single center retrospective study reported on germ cell malignancies in 18 children with TS+Y who received gonadectomies between 2012 and 2021 at a median age of 7.4 years.[14] The authors assert this is the largest study of children with this trait, and they suggest that delaying gonadectomy "for any reason" is unsafe, based in large part on their identification of a gonadal blastoma (a premalignant germ cell tumor) at the age of 40 days in 1 of the 18 children.

However, the authors acknowledge the study's inherent vulnerability to selection bias and confounding, as well as the lack of a non-intervention comparison group. They also acknowledge the need to "weigh the potential risk of malignancy with the rare prospect of fertility and hormonal function sufficient for menarche or pubertal changes," suggesting that a delay could, in fact, potentially be of benefit, consistent with the view of K's parents.

In K's case, regular ultrasound surveillance has already been initiated. While a surgical biopsy would provide more data on gonad tissue-type to assist with risk assessment, the parents have ruled it out. There is an additional factor here, which should have been taken into account prior to the cardiac surgery. Risks to children can accrue from early exposures to general anaesthetic,[15]

meaning that any additional early surgery may have developmental consequences for the child beyond questions about gonadal tumor risks and puberty.

With the absence of a clear and unambiguous evidence base to justify a non-voluntary gonadectomy in this case, it is not unreasonable for parents to give significant weight to the value of protecting their child's future sexual and reproductive autonomy. On this view, gonadectomy ethically may -- perhaps even should -- be deferred until the child can at least participate in the decision-making process concerning such surgery. In the meantime, continued risk management via regular ultrasound surveillance is warranted and is supported by the parents.

Prof Dominic Wilkinson

The key ethical question in this case is whether a decision to forego (or delay) surgical removal of gonadal tissue lies within the "zone of parental discretion."[16] That concept refers to the range of permissible, sometimes medically suboptimal, choices that pediatricians and society allow (and should allow) parents to make. It is, of course, crucial that decisions are made with the child's best interests in mind. But there may be more than one decision that would potentially promote those interests.

While there is wide support within and between cultures for granting parents some degree of discretion and choice in relation to medical treatment for their children, the difficulty is in

working out where are the limits to that discretion. One familiar and broadly (though not uniformly) shared notion is that the zone of parental discretion is bounded by a harm threshold – the point at which the parents' choice would pose a significant risk of serious harm to the child.[17] On that model, the question shifts to whether the risk of gonadoblastoma and malignant transformation in conservative management of TS+Y poses such a significant risk, or does not.

One of the difficulties here is highlighted by Earp et al. and by Dr Ho. The nature of available evidence makes it impossible to know what the statistical chance of transformation is. This is an example of the epistemic problems arising from what we could call a self-negating prophecy.[18] Past predictions of malignancy have led to interventions that thereby remove the risk. But that then makes it impossible to know if the original prediction was correct (or in what proportion of cases).

There is, however, a deeper problem. It is unclear what level of risk would be sufficiently low to support parental choice, or sufficiently high to warrant overruling parents.

The scientific uncertainty in this case obscures this question, but we could hypothetically imagine that is resolved. It seems plausible that over the next decade there will be more experience of conservative management of TS+Y. Imagine that a review of that experience performed in 2039 indicates (as predicted by the upper margin of existing estimates) that 6% of children managed without gonadectomy develop gonadoblastoma with malignant transformation over the course of childhood.

At that point, pediatric endocrinologists and ethicists might debate in the pages (or e-pages) of this journal whether such a risk is sufficiently high that parents should not be permitted this option. Whether it is or not will depend on some further medical facts, including how easily treatable malignant gonadal tumours are in 2039, and the consequences of such treatment. It will also depend on how significant are the benefits of delaying surgery. It is clear that some children and adults with intersex conditions who have had surgery in early life have subsequently expressed regret and anger at having a choice taken from them that they (in later life) regard as highly significant. We might have more information in 2039 on how valuable children and young people with TS+Y view having had the later choice of gonadal removal, and the possibility of natural puberty induction against the risk of malignancy. If that choice is very important to them, that might support the conservative option.

There is a further consideration. We will need to factor in the willingness of a society (and its legal system) to intervene and impose surgery in the setting of uncertainty. If there is a 6% risk of serious negative consequences, that means that it would be necessary to overrule 16 parents for one child to benefit. Some legal systems might regard that as acceptable. Others, I suspect, will see this as unacceptable. In other settings, courts will only reach judgements if the statistical threshold is 50% (balance of probabilities) or higher.

In the short term, in the absence of clear evidence to support the traditional practice, parents' choice to defer surgery seems to fall within the zone of parental discretion. If that is the conclusion of the clinical team, it would be important to minimize and mitigate the risk to K. The suggestion of a gonadal biopsy is one compromise option. (One additional question is whether

such a biopsy might also be useful in predicting subsequent gonadal function.) But if, as appears to the be case, parents do not wish that, close ultrasound surveillance offers a way to detect any changes as early as possible and help clarify whether surgery is necessary and the timing of that surgery.

One final note: it appears unlikely on the basis of the description of the parents' views in this case. But we might imagine another set of parents who are opposed to surgery in any circumstances, perhaps preferring traditional remedies or resort to prayer, even in the face of ultrasound evidence of a gonadoblastoma. In that case, there would be good reason to think that the harm threshold had been crossed or would be crossed by further waiting. Legal options for safeguarding the wellbeing of the child should be pursued.

Outcome of case

Regular ultrasound surveillance is arranged for K and the scans have remained normal so far. The first author will be monitoring the child's growth and onset of puberty to determine gonadal function.

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