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Female fertility preservation in DSD

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Disorders of sex development (DSD) are a group of complex conditions that can affect chromosomal, gonadal, and/or phenotypical sex with a highly variable fertility potential amongst affected individuals. In this review we discuss fertility issues facing patients affected by DSD and Turner syndrome and summarise the literature on fertility and reproductive outcomes. We will also discuss fertility preservation prior to gonadotoxic treatment in adolescent and prepubertal girls. Future directions in fertility preservation and ethical issues will also be addressed. Fertility preserving options that are established include ovarian tissue and oocyte cryopreservation. However, in many of the DSDs fertility is not possible and the discussion may need to move toward alternative methods of creating a family such as gamete donation or surrogacy.

Introduction

The term “disorders of sex development (DSD)” encompasses a variety of clinical conditions with varying effects on fertility. Individuals with such disorders have incongruence between chromosomal, phenotypic and gonadal sex. Fertility rates vary widely. Many of these disorders are rare, with reports

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of fertility sporadic and by case series only [1]. Fertility may be compromised by the abnormal production of hormones, abnormal development of the gonads or as a result of medical treatments such as gonadectomy. In many of these disorders fertility is not possible, thus turning the conversation from one of fertility preservation to one of alternative methods of creating a family such as through gamete donation, surrogacy, fostering or adoption.

Disorders of sexual development with 46 XX karyotype (46 XX DSD)

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder most often characterized by 21-hydroxylase deficiency. It is one of the most common causes of ambiguous genitalia and a masculinised female at birth. Phenotypically, children with 46XX CAH are born with varying degrees of ambiguous genitalia. Prompt diagnosis and management is essential to avoid morbidity from a salt losing crisis.

Reported fertility rates vary but depend on severity of disease and degree of control [1,2]. Classic salt wasting CAH is associated with fertility rates between 0 and 10%, whereas simple masculinizing CAH has reported rates of up to 50% [1]. There are scant reports of fertility in the rarer variations of CAH such as 11B hydroxylase deficiency [3]. The causes for subfertility vary, but poorly controlled CAH may result in anovulation. Psychosexual factors may also play a role as several studies have noted that women with CAH have later sexual debut, dissatisfaction with their genitals and fewer living in steady heterosexual relationships [4–6].

Non-classical CAH (NCCAH), due to a partial enzyme defect, is associated with higher fertility rates [2] with some reports of subfertility being comparable to the general population [6,7]. Menstrual irregularity is a common symptom in both women with NCAH and those with subfertility, and the diagnosis of NCCAH may be made whilst under investigation for subfertility.

There is scant research addressing fertility preservation in this population. Excellent disease control is essential, both for long-term health and fertility. Glucocorticoid treatment suppresses adrenal androgen over-secretion, in turn normalizing the pituitary-ovarian axis to allow for ovulation. Subfertility rates are higher in those patients with suboptimal control, partially due to suboptimal ovulation, and patients wishing for fertility should be counseled regarding this.

Women with CAH are not immune to the natural decline in egg quality and fertility with age. As for any woman, they should be educated regarding this and options such as elective egg freezing discussed and offered when appropriate.

Mayer Rokitansky Kuster Hauser syndrome

Mayer Rokitansky Kuster Hauser syndrome (MRKH) is characterized by varying degrees of Mullerian agenesis. There are case reports of rudimentary uteri with uterine cavities undergoing neovaginoplasty but no case reports of pregnancy [8]. For this group of patients, pregnancy will only be possible via ovarian stimulation, oocyte retrieval and the use of a gestational surrogate [9]. Discussion and counseling regarding fertility options forms an essential part of care for these patients [10].

Disorders of gonadal differentiation

Turner syndrome

Turner syndrome (TS) is characterized by partial or complete loss of one of the X chromosomes and may be either complete (45X0) or mosaic (46XX/45X0). It is estimated to affect 1 in 2000 live born females [11]. A common feature is ovarian failure, occurring prior to the onset of puberty in 70–90%. Patients with a mosaic pattern are more likely to have spontaneous onset of menses but progression to premature ovarian failure is almost inevitable [12]. Despite this, there have been many reports of spontaneous pregnancy in women with Turner syndrome, with rates of around 2–5% [13–15].

Few studies have investigated the outcomes of such spontaneous pregnancies, but suggest that both mortality and morbidity are increased for both mother and baby, predominantly as a result of cardiovascular disease [16,17]. In addition, spontaneous pregnancies in women with TS are associated with increased fetal anomalies of up to 20%, miscarriage rates of 30% and up to 7% perinatal death rate.

Studies investigating Turner syndrome patients pregnant via oocyte donation have found up to 60% suffer complications [18]. Hypertensive disorders are common, affecting up to 40% of patients, and often resulting in the development of severe pre-eclampsia and preterm delivery, Intrauterine growth restriction and prematurity occurs in up to 50% [18,19].

Of most concern is the risk of aortic root dilatation and subsequent aortic dissection. Women with Turner syndrome are at a higher risk of aortic root dilatation, and pregnancy itself may be a risk factor due to increased blood volume and cardiac output. This catastrophic event puts both mother and baby at risk, with several reports of perinatal death as a result. Pre-pregnancy cardiac investigations may not necessarily predict future risk and pregnancy should only be attempted after thorough cardiac review and investigation, with a multidisciplinary team and facilities who are able, and willing, to look after the pregnant patient and her baby. Frank discussions with the patient regarding the risk pregnancy could pose to her health are essential. Pre-existing conditions such as known aortic root dilatation, uncontrolled hypertension and so on should be considered contraindications to pregnancy and the patient counseled as such. The possibility of ovum donation and surrogacy should be considered as a safer alternative in these situations. The conversation regarding the pros and cons of fertility preservation must include the potential medical risks to the mother and fetus. These risks may evolve over time and must be regularly reassessed before proceeding with a recommendation for either fertility preservation or pregnancy.

The possibility of fertility preservation exists in those women with Turner syndrome where some ovarian function exists. This is mostly relevant to the women with mosaic 45 X/46XX mosaic genotype as ovarian primordial follicle reserve is depleted in nearly all girls with 45X karyotype well before puberty. It has been proposed that assessment of ovarian reserve in the mosaic group is appropriate, followed by appropriate counseling and pursuit of either ovarian tissue freezing or oocyte cryopreservation. It has been recommended that pre-pubescent girls with Turner syndrome have their serum anti-Mullerian hormone levels assessed. If within the normal range, it should be repeated, with ovarian tissue cryopreservation considered if there is a consecutive drop in the AMH. If the AMH is low at first assessment, ovarian tissue cryopreservation could be considered. In many cases this involves removing an entire ovary considering the already low ovarian reserve [20]. Of concern in this group is the possibility that the process of fertility preservation (whether through ovum or ovarian tissue preservation) will accelerate ovarian failure thus subjecting them to the need for hormone replacement therapy (HRT) earlier than may otherwise be necessary. In the post pubertal population the rate of follicle depletion is high and fertility preservation could be considered regardless of the initial AMH. Controlled ovarian stimulation followed by transvaginal ovum pick up under sedation is appropriate and usually well tolerated in this age group. Even in this young population, the ovarian reserve may be exhausted in which case fertility preservation is not an option and counseling should address alternatives for future family creation including egg or embryo donation or adoption.

The success of fertility preservation in women with Turner syndrome is not well documented. There are reports of between 4 and 11 mature oocytes being obtained through one stimulation cycle [21] but no reports of successful pregnancies as a result of autologous frozen oocytes or ovarian tissue. Due to a slightly higher aneuploidy rate in oocytes, it is expected that not all oocytes will be suitable to fertilize or develop a normal karyotype. There is a reported increased risk of fetal anomalies, particularly brain and heart anomalies, of up to 20% [16] which is an important consideration of the risk to offspring.

Mixed gonadal dysgenesis

Individuals with mixed gonadal dysgenesis most frequently have a 45X/46XY karyotype, a unilateral streak gonad and contralateral, dysgenetic testis. Infertility is considered universal [1]. There is an estimated risk of malignancy in the streak gonad in the order of 10–15% and prophylactic removal is

recommended. Germ cells have been found in these gonads, however the successful utilization of such germ cells is yet to be established [22]. The potential for germ cell preservation therefore exists, but at this stage is still experimental.

Ovotesticular DSD

Ovotesticular DSD is characterized by the presence of both ovarian and testicular tissue. It is an uncommon condition, occurring in less than 10% of DSD cases [23]. Genital appearance varies and is dependent on the type and function of the gonadal tissue present. Karyotype is most frequently 46XX although mosaicism is frequent. A small number of pregnancies have been reported in ovotesticular DSD females [24]. Little is known about fertility preservation in this group, but wishes for fertility should be considered and discussed prior to gonadectomy [25].

46XY gonadal dysgenesis

This rare variation of pure gonadal dysgenesis affects around 1 in 80,000 individuals and is characterized by normal external female genitalia, uterus and fallopian tubes and bilateral streak gonads. These gonads have high potential for malignancy, with up to 30% developing a dysgerminoma or gonadoblastoma [23] and therefore early removal is warranted. Pregnancy with donor eggs or embryos may be possible, but fertility preservation by the way of egg freezing is not feasible.

Disorders of sexual development with 46 XY karyotype

Androgen insensitivity syndrome

Complete androgen insensitivity syndrome (CAIS) is characterized by 46 XY karyotype in a person with normal female external genitalia, varying degrees of vaginal agenesis, an absent uterus and intra-abdominal testes. It is included in this review as the majority of patients with CAIS have a female phenotype and are raised as such. Spontaneous pregnancy is not possible. Germ cells have been detected in the intra-abdominal gonads [26]. raising the possibility of future fertility. The gonads may play a role in fertility preservation, but at this stage it is purely speculative and experimental [22]. There is a small risk of gonadoblastoma in the intra-abdominal testes, around 2–16% over a lifetime. Prior practice was to remove them early in life, however more recent evidence suggests they may remain until after puberty allowing for optimal development and allowing the more mature patient to better understand and participate in their health care decisions [27].

Partial androgen insensitivity syndrome (PAIS) presents with variable phenotypes of ambiguous external genitalia. Many are raised male and the most common phenotype includes severe hypospadias, cryptorchidism and rudimentary Wolffian structures. Infertility is common. Sexual function may be altered by varying degrees of hypospadias and histological examination of the gonads reveals a sparsity of spermatocytes and spermatids [28]. The options for fertility preservation in these individuals are limited.

Female fertility preservation: pre gonadotoxic treatments

Introduction

Currently, there are both clinically approved and experimental fertility preservation options available to young girls and women facing gonadotoxic therapies to treat cancer and autoimmune conditions [29]. It is known that young people with cancer are interested in discussing fertility preservation and it is an important aspect of their future quality of life. Therefore, health care providers should address the possibility of infertility with them as early as possible before treatment starts to optimise their long-term success. All young patients facing gonadotoxic

treatment should have the opportunity to be referred to a reproductive specialist to have this discussion [30].

There are concerns that there is an increasing number of cancer diagnoses among young women of reproductive age eg melanoma, breast cancer, colorectal cancer rates are rising [31]. Often treatments with these cancers can be associated with rates of permanent amenorrhoea of up to 90%. At the same time survival rates have increased, reaching almost 90% due to advances in early detection and therapy with more patients surviving long term [32,33]. As a consequence, there is an increasing need for fertility preservation amongst these patients, for whom it is a vital aspect of their long term physical and emotional wellbeing. It is also viewed by young cancer patients as a quality of life priority [29].

Gonadotoxic treatment such as chemotherapy, radiation and partial or complete gonadectomy are used to treat many malignancies in young women. High intensity multi-modality treatments such as alkylating chemotherapy agents (eg cyclophosphamide, busulfan), radiation therapy (pelvic, whole abdomen, cranial and total body irradiation) and stem cell transplantation have a high associated risk of premature ovarian insufficiency with associated loss of fertility.

Women facing gonadotoxic treatments

Female fertility may be impaired following surgery, chemotherapy, or radiotherapy treatment for cancer [34]. The age of the patient is an important determinant of their risk of premature ovarian insufficiency (POI) as a result of gonadotoxic therapy [32].

Ovarian damage is drug- and dose-dependent and is related to age at the time of treatment, with progressively smaller doses producing ovarian failure as the patient's age increases [35]. Total body, abdominal, or pelvic irradiation may cause ovarian and uterine damage, depending on radiation dose, fractionation schedule, and age at the time of treatment. An elevated serum follicle-stimulating hormone (FSH) level was the most traditional biochemical indicator of ovarian damage and failure. However, serum anti Mullerian hormone (AMH) and antral follicle count (AFC) are now commonly used as more accurate markers of ovarian aging (ASRM).

Younger women exhibit better outcomes of fertility preservation as well [32]. Chemotherapy and radiation can cause accelerated depletion of the primordial follicle pool, induce atrophy and fibrosis of the ovarian cortex and disrupt gonadal blood supply [36]. The effect of different chemotherapy regimens can be highly variable. For instance, standard first line treatment of Hodgkin's lymphoma is ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine), which is considered to have a low risk of POI in reproductive age women (<10%). However, patients undergoing regimens containing alkylating agents or hematopoietic stem cell transplant (HSCT) are strongly advised to consider fertility cryopreservation, having a POI rates of 80–100%. The chances of becoming pregnant by spontaneous conception after these treatments can be very low and are thought to be 3–8% [36].

Cranial irradiation may lead to disruption of the hypothalamic-pituitary-gonadal axis, with consequent dysregulation of the pituitary dependent hormonal secretion. The uterus can also be damaged by radiotherapy. Particularly exposure to radiation during childhood leads to changes in uterine and endometrial blood supply, decreased uterine volume and elasticity, fibrosis of the myometrium and necrosis, endometrial atrophy, which all have significant impact on the ability to carry a pregnancy. As radiation has a relevant impact on reproductive potential, fertility preservation procedures should ideally be carried out before treatment commences [37].

Fertility preservation options

GnRH agonists

There is conflicting evidence to recommend gonadotropin-releasing hormone agonists (GnRHa) and other means of ovarian suppression for fertility preservation. The proposed mechanism of action includes hypogonadotrophic hypogonadism induced ovarian dormancy and associated reduction of ovarian blood flow [32].

The protective effect of GnRH analogue cotreatment during chemotherapy is quite debatable. There are multiple conflicting meta-analyses in the literature. A meta-analysis by Elgindy et al. [38] of ten

randomised controlled trials, assessed GnRH agonist efficacy for ovarian protection in women with breast cancer or lymphoma. The evidence was limited by heterogeneity between studies. The results suggested that gonadotropin-releasing hormone analogue co-treatment did not significantly increase ovarian function resumption nor was there a protective effect even after subgroup analyses for type of malignancy. Contrary to this, Senra [39] et al. in their meta-analysis of randomised controlled trials showed GnRH agonists had a significant benefit on the risk of premature ovarian insufficiency/amenorrhoea which persisted in the subgroup analysis for breast cancer but not lymphoma. They also showed a higher rate of spontaneous conception after completion of treatment in women receiving GnRH agonist. Overall the quality of their evidence was also low. All included studies were in adult women, and the available data may not be completely representative of outcomes in younger survivors who may not yet be of an age to reproduce. Wallace et al. showed that very few girls and young women will actually develop premature ovarian insufficiency post gonadotoxic therapy and they developed the Edinburgh selection criteria to identify these females. Overall their results showed the percentage is low and therefore raises the question if GnRH analogues are valid in these young women [40].

The results of this analysis show that the Edinburgh selection criteria accurately identify the few girls and young women who will develop premature ovarian insufficiency, and validate their use for selection of patients for ovarian tissue cryopreservation.

The American Society of Clinical Oncology recommends that when proven fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced premature ovarian insufficiency. However, GnRHa should not be used in place of proven fertility preservation methods [30,41].

Oocyte cryopreservation

Oocyte cryopreservation was deemed a non-experimental fertility preservation method by the American Society of Reproductive Medicine (ASRM) in 2013 [42].

It is a well established technique in the management of infertile patients with assisted reproductive technology (ART) [32], with considerable data in the literature regarding the efficacy of oocyte cryopreservation for egg donation treatment. Results reported by Cobo et al. suggest that the cumulative birth rates of 10 and 15 oocytes cryopreserved for non-oncologic reasons were 60.7 and 85.2%, respectively and that survival rates from frozen eggs range from 86 to 97% [43,44]. It should be noted that these statistics are quoted by a group considered to be expert in the area of oocyte vitrification and that results can vary between centres. Such data from oocyte freezing for ART has largely been used to counsel oncology patients about the pregnancy potential of their frozen oocytes.

Flexible ovarian stimulation protocols are available, such as random start protocols, so the procedure does not depend on the start of the menstrual cycle and can be initiated without delay [30].

Random-start stimulation has been associated with a reduced time interval between ovarian stimulation and oocyte or embryo cryopreservation. The yield of mature or MII (metaphase 2) oocytes and their developmental potential into embryos was comparable between conventional and random-start protocols, but with higher gonadotropin doses used in the latter [45].

Despite its success in adult women, there remains a limited number of publications that discuss ovarian hyperstimulation and oocyte retrieval for post-pubertal children receiving fertility-threatening therapy [29]. The youngest patient reported to successfully undergo oocyte retrieval and cryopreservation was 13yo. In addition there was a wide range of success in terms of the number of MII (metaphase II) oocytes cryopreserved in these children. Some reports of successful in vitro maturation have also been reported in adolescent patients and this might be an area of future development.

Complications of oocyte retrieval are generally low, but there is the potential for damage to pelvic structures, blood vessels and viscus injury. The more common side effect is ovarian hyperstimulation syndrome (OHSS) particularly in young women with a high ovarian reserve. OHSS can not only cause morbidity such as ascites, pain, nausea, deep vein thrombosis, pulmonary embolus and hospital admission but can delay commencement of cancer therapy. The use of GnRH antagonist protocol with GnRH agonists trigger in ovarian stimulation has been shown to significantly reduce the incidence of OHSS and is recommended practice.

Embryo cryopreservation

Embryo cryopreservation is a well established fertility preservation method, and it has routinely been used for storing surplus embryos after in vitro fertilization [30]. The stimulation protocol is the same as that for oocyte cryopreservation, and after controlled ovarian hyperstimulation, oocytes are collected transvaginally or transabdominally if indicated. Oocytes are then fertilised with the woman's partner's sperm. Vitrification, the same technique as egg freezing has been applied to embryos with good survival when warming of upto 95% [32].

This method of fertility preservation is not an option for young adolescent women for obvious reasons, but reassuringly with excellent oocyte freezing success rates, their chances at future pregnancy are not significantly compromised by not being able to freeze embryos. Embryo freezing has unique ethical and legal considerations, in some countries embryo cryopreservation is legally prohibited. Also frozen embryos belong to the couple and cannot be used by the woman if the relationship terminates before she returns to use the embryos without consent.

Ovarian tissue cryopreservation

Although still classified by the ASRM as an experimental technique, in expert centres ovarian tissue grafting is advancing at a rapid pace. Ovarian tissue is obtained laparoscopically by undertaking a partial or total oophorectomy. The tissue is then sliced into strips and assessed for the density of primordial follicles. A specimen is also sent for histological assessment to detect malignancy. The tissue is then either cryopreserved by slow freeze or vitrification.

The benefit of tissue cryopreservation is that it can be obtained immediately without delaying the patients' chemotherapy/treatment and does not involve the risk of OHSS. This is the only method available to prepubescent girls at present [29,30]. It can be combined with oocyte or embryo cryopreservation if the patient wishes. It also offers the advantage of return of ovarian endocrine function and may be an area of future use aside from fertility. Depending on the location of the ovarian tissue graft, and the condition of the fallopian tubes and uterus, it is the only option that allows women a chance at natural conception. When a patient wishes to use her harvested ovarian tissue, the ovary is grafted back either into the abdominal wall or in the pelvic side wall in a peritoneal window or on the ovarian medulla. The woman then undergoes a few months of observation to assess for return of ovarian endocrine function and then gentle stimulation with gonadotrophins to stimulate follicles and oocyte development from the tissue. Currently auto-transplantation of ovarian tissue obtained from patients with leukaemia or neuroblastoma is contraindicated, with unspecified risks for some other tumours. There must be very careful consideration of the chance of tumour transfer prior to consideration of this technique. Various methods are being used to evaluate tissue for the presence of malignant cells, such as histology, immunohistochemistry, FISH, next-generation sequencing, and xenotransplantation with some promising results in mouse models. One group has reported a successful case of harvesting of ovarian tissue during complete remission in a young woman with acute myeloid leukaemia, with intense tissue evaluation before bone marrow transplantation and subsequent livebirth [46]. This area continues to evolve.

As of Jan 2018, more than 130 live births have been reported from ovarian tissue grafting. It is difficult to establish a pregnancy rate, as the number of transplantations performed worldwide is not known. However, live birth rate are estimated, based on the results of several case series as 25–35% [34]. Major problems faced by groups have been ischemic damage to the tissue pending transplant and redevelopment of a blood supply in the graft and the theoretical possibility of reintroducing malignant tumour cells in blood borne cancers such as leukaemia [42].

Ovarian transposition

Ovarian transposition or oophoropexy can be performed prior to pelvic radiation or spinal chemotherapy as a cancer treatment. It does not offer the ovary any protection from chemotherapy. The procedure can be performed either laparoscopically or by laparotomy. This does not protect the ovaries

from radiation scatter and patients should be counseled this treatment is not always successful [30]. The ideal time for the procedure is just before radiation therapy to avoid remigration of the ovaries into the field of treatment. The failure rate is quoted at 31% for this procedure [47]. Complications associated with this procedure are rare but includes small bowel obstruction, dyspareunia if ovaries are transposed into the pouch of Douglas, functional ovarian cysts and pelvic adhesions [29].

Ethical issues

The ethics of fertility preservation for DSDs and in young women facing gonadotoxic therapy is extremely important with various factors to consider. With some DSDs and a history of certain types of cancers, pregnancy can not only increase maternal morbidity and mortality in the antenatal and postnatal period but may also increase the recurrence risk of certain malignancies. It is also important to ensure when undertaking fertility preservation procedures that the patients morbidity and mortality is not adversely affected by the treatments. The ethical issues involved will be briefly discussed below.

One important issue that applies to both groups, ie patients with DSD and young women facing gonadotoxic therapies is the ability of minors to consent and their parents to do so on their behalf. Another issue is the risk to offspring. Some DSDs are associated with genetic defects that can be passed onto offspring. With patients facing cancer therapy it is generally deemed by professional fertility societies that long term concerns about the welfare of offspring in women who have had gonadotoxic treatment is not a sufficient reason to deny patients fertility preservation.

For many years, counseling regarding fertility in patients with DSD has centered around the inability to conceive. With advances in reproductive technology and knowledge about these conditions, the conversation should change to assess each individual's reproductive potential. Consideration needs to be made to the age of the patient with the DSD, their ability to understand and consent to the procedure or, alternatively, the appropriateness of their parents or caregivers to make these decisions.

Oocyte and ovarian tissue freezing are established procedures that may be offered. However, such procedures in the DSD populations are still under study and are by no means a guarantee of future fertility. Realistic expectations should be set rather than giving a false sense of hope. Many of these procedures are in their infancy and their feasibility yet to be fully established in the DSD population.

The suitability for pregnancy needs to be taken into account when considering an individual with DSD for fertility preservation. Some conditions, Turner syndrome in particular, may be associated with other medical conditions for which pregnancy is high risk or contraindicated. Such conditions may evolve over time and not be apparent at the time of fertility preservation. Ongoing assessment of such conditions, involvement of obstetric physicians and alternatives, such as surrogacy, should be considered early in the discussion. Likewise many DSDs have a genetic basis and this needs to be taken into account regarding the risk to any offspring.

The suitability for pregnancy needs to be taken into account when considering an individual with DSD for fertility preservation by weighing up the risks and benefits. Some conditions, Turners syndrome in particular, may be associated with other medical conditions for which pregnancy is high risk or contraindicated. Such conditions may evolve over time and not be apparent at the time of fertility preservation. Careful counseling of the patient and their partner is required in a multidisciplinary team environment with reproductive endocrinologists, cardiologists, maternal fetal medicine specialists and genetic counsellors.

Various organisations have published ethical guidelines on the provision of fertility preservation to young patients facing gonadotoxic treatment. Key points are that all available options of fertility preservation should be offered to patients and can be performed alone or in combination without causing significant delay or compromise to cancer treatment.

However the important ethical issues pertain to experimental compared to established therapies, the ability of minors and their parents to give consent, the welfare of future offspring, and posthumous use of gametes/ovarian tissue. The issue of consent in minors is important and it would seem practical that parents can consent to preserve the reproductive potential of their children as long as the intervention does not pose undue risk and offers a reasonable chance of benefit to the child in the future. It is vital that fertility centres storing gametes, embryos or ovarian tissue have clear

documentation of the management of the tissue in the event of death, uncontactability or lack of payment of storage fees if indicated. Posthumous use will be subject to local jurisdictions and laws the discussion of which is beyond the scope of this paper.

It is also essential that fertility preservation treatment should not negatively affect the prognosis of the cancer. In estrogen-sensitive breast and gynaecologic malignancies there is the possibility that ovarian stimulation regimens that increase estrogen levels may increase the risk of cancer recurrence or disease spread. Aromatase inhibitor–based stimulation protocols are now well established and may provide reassurance to patients and clinicians. Studies do not indicate increased cancer recurrence risk as a result of aromatase inhibitor–supplemented ovarian stimulation and subsequent pregnancy [32,48].

Lastly, another key concern is that some of the outcomes of fertility preservation for cancer patients are just estimated at present based on the results obtained from cryopreserved embryos and oocytes for non-oncologic reasons, by assuming that the outcomes of cancer patients are comparable to non-cancer patients. However, it is still controversial whether this assumption is true [32].

Future directions

The field of fertility preservation is progressing rapidly due to advances in assisted reproductive treatment and an increasing demand for the service. Some promising treatments that may give these patients more options in the future are in vitro maturation (IVM), artificial ovary model and in vitro activation (IVA).

IVM refers to the collection of immature oocytes without any prior ovarian stimulation. It is still considered experimental, however is an option when chemotherapy cannot be delayed or if ovarian hyperstimulation is a major concern. It can be done at any phase in the menstrual cycle. Live births have been reported from IVM in fertility preservation patients however it is reported that when comparing IVM to conventional IVF, a lower number of oocytes and embryos are cryopreserved and live birth rate is lower [49].

Some groups have been working to create an artificial ovary as an alternative way of restoring fertility in patients who cannot benefit from transplantation of cryopreserved ovarian tissue due to the risk of reintroducing malignant cells. The concept of the artificial ovary is to graft preantral follicles and ovarian tissue in a fibrin three dimensional scaffold. Survival and growth of isolated murine ovarian follicles has been demonstrated and a proven xenograft model is awaited [36,50,51].

New treatments are also emerging for premature ovarian insufficiency that may benefit cancer patients who did not have the opportunity for fertility preservation prior to treatment. A fertility treatment called in vitro activation (IVA) pioneered by Kawamura et al., enables patients to conceive using autologous eggs by activation of AKT signalling pathway in the ovary. This is thought to activate any residual dormant primordial follicles in the ovary, which are thought to exist even in women with POI. Currently this group has reported 2 live births in patients with POI. Whether this technique can be applied to cancer patients remains to be seen [52].

Practice points

- Fertility preservation by oocyte cryopreservation in post pubertal and adult women is routine practise.
- Fertility preservation by ovarian tissue cryopreservation and autografting is considered experimental, but there have been over 130 live births and the area is rapidly advancing.
- Ovarian tissue cryopreservation is the only option for prepubertal girls facing gonadotoxic treatment.
- Fertility preservation in DSD still has limited options and the cause of infertility is multifactorial. A discussion should be focussed around alternate ways to create a family such as gamete donation, surrogacy, adoption.
- Future developments such as IVM, in vitro activation and xenograft models may increase options available to young women.

Research agenda

- Development of a safe way to use cryopreserved ovarian tissue in patients who are at risk of reintroduction of malignancy eg leukaemia. Future research should focus on xenograft models or artificial ovary development.
- The use of genomic editing technology such as CRISPR, in patients with DSD who may be at risk of transmission of genetic defects to their offspring.
- Further development of In vitro maturation to obtain mature oocytes from ovarian tissue in prepubertal and postpubertal women.
- Data collection on the fertility aspirations of patients with DSD to enable better provision of multidisciplinary services to meet their needs.

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