Review

Long-term health issues of women with XY karyotype

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ABSTRACT

46XY women is a label that gathers together a number of different conditions for which the natural history in to adult life is still only partially known. A common feature is the difficulty that many women encounter when approaching clinicians. In this review we assemble medical, surgical and psychological literature pertaining adult 46XY women together with our experience gained from an adult DSD clinic. There is increasing awareness for the need for multidisciplinary team involving endocrinologist, gynaecology, nurse specialist and particularly clinical psychologists.

Management of adult women with a 46XY karyotype includes several aspects: revising the diagnosis in those with previously incomplete workup; exploring issues of disclosure of details of the diagnosis. Surgery needs to be discussed when the gonads are still in situ and when partial virilisation of genitalia have occurred. To maintain secondary sexual characteristics, for general well being and for bone health, most women require sex steroid replacement continuously until the approximately age of 50 and it is important that the treatment is tailored on individual basis. Women should have access to advice about fertility options involving egg donation and surrogacy.

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1. Introduction

From the earliest moment in life we are each engrained with the notion of binary sex. Only for fleeting moments might we question the solid basis of our sexual development. As clinicians we may never know how it might feel to have one component of sexual identity differ from the usual pattern and there is a history in medicine of unwittingly causing harm by handling this topic in an insensitive if not brutal manner.

Medical textbooks describe the classical triad of criteria for disorders of sexual differential defined as any incongruence between genetic, gonadal and genital sex. A variety of genetic mutations lead to an XY karyotype in women and the rarity of these conditions often leads to delay both in diagnosis and access to an experienced care team. These issues often compounds the experience of "feeling like a freak" and leads to a sense of uncaring consultations with the medical profession.

In this review we will consider issues that arise for women who have an XY karyotype based on clinical experience. Women with a Y chromosome share some of the difficulties common to routine gynaecology practice but the component of gender can be fundamental to accepting the condition. Failure to address this at an early stage and to provide ongoing support is still commonplace in medical practice.

The content of this review is based on the experience gained from an adult DSD clinic of 15 years standing. UCLH DSD clinic is a tertiary referral centre for disorders of sex development and it is organized as a multidisciplinary team. Clinical management involves an endocrinologist, a gynaecologist, clinical psychologists and nurse specialist with additional input from specialists in reconstructive surgery, urology, fertility, sex therapy and geneticists as required. Perhaps the key role in the care of 46XY females is performed by specialized psychologists who deal with the emotional side of these conditions. The team strive to coordinate psychological, surgical, medical and fertility issues of DSD on an individual basis.

Much of the literature relating to DSD comes from paediatric practice [1–4] and the adult perspective is not commonly presented. Children with DSD often transition from specialist paediatric care to general adult services or to primary care with consequent loss of confidence in medical services. After losing contact with medical care it can often be difficult to find a way back to an informed clinical service.

There are many components to the care of 46XY females and the aim of this review is summaries the diagnostic process, disclosure, gonadal malignancy risk, long-term hormonal replacement therapy, psychological issues and reproductive issues as currently addressed in our practice.

2. Definitions and terminology

Until recently 46XY females were referred with terms such as "intersex", "pseudohermaphroditism", "sex reversal", "hermaphroditism" and gender-based diagnostic labels. The Consensus Statement on Management of Intersex disorders 2006 presented a now widely accepted system of nomenclature and proposed the umbrella term of "Disorders of Sex Development" or DSDs, proposed it [6]. Table 1 summarises this system of categorisation. Exhaustive reviews [7] have described genetic background to DSD conditions, we present them for reference in Table 2.

Clinically, the phenotype of 46XY females in an adult clinic can be grouped in three major categories according to the presence of uterus and other mullerian derivatives.

- 46XY females who develop with functioning testis producing antimullerian hormone (AMH) are born without uterus. AMH is

Table 1
A summary of the new nomenclature relating to disorders of sexual development.

Previous	Current
Intersex	Disorder of sex development (DSD)
XY sex reversal	46,XY gonadal dysgenesis
Male pseudohermaphrodite	46,XY DSD
Undervirilisated XY male	
Female pseudohermaphrodite	46,XX DSD
Masculinised of XX female	
True hermaphrodite	Ovotesticular DSD
XX male, XX sex reversal	46,XX testicular DSD

produced by Sertoli cells in early gestation and causes the dedifferentiation of the mullerian duct system. Women affected by Androgen Insensitivity Syndrome (AIS), 5 alpha reductase (5AR) deficiency and 17β hydroxysteroid dehydrogenase (17β-HSD) deficiency fall in this category.

- 46XY females without a function testis – with gonadal dysgenesis – do not produce AMH allowing the mullerian duct system to differentiate to form a uterus. The mesonephric ducts fails to develop in the absence of testosterone, and the undifferentiated urogenital sinus and external genitalia mature into female structures. Women with 46XY Gonadal Dysgenesis or Swyer's Syndrome form the majority of this group.

- 46XY women with ovotesticular DSD who have variable testicular function resulting in unpredictable secretion of AMH have variable uterine appearance. For example, a hemiuterus may develop if testicular tissue is predominantly unilateral.

In Table 3 we present the profile of cases attending a tertiary DSD clinic at UCLH to give some idea of the relative frequency of various diagnostic groups. In most instances the diagnostic label is based as clinical criteria with only a proportion having genetic confirmation.

3. Clinical presentations

In practice, the experience for a 46XY female is determined by the age of presentation and here we consider the common patterns.

3.1. Diagnosis in utero

The earliest presentation arises in utero with those where ultrasound appearances differ from genetic information obtained from amniocentesis. Any of the diagnostic groups may present in this way and this will undoubtedly be a more common group in the future. Approximately 5% of women with complete AIS (CAIS) in our clinic were diagnosed in this way.

3.2. Ambiguous genitalia at birth

A common presentation that is covered extensively in paediatric literature is the child is born with ambiguous genitalia [4,5,2]. In the presence of a Y chromosome, a degree of virilisation at birth implies the presence of a functioning testes and the likely production of AMH so in this situation the uterus is likely to be absent. The most common diagnoses in this presentation group include partial AIS (PAIS), 5AR deficiency, 17β-HSD deficiency.

3.3. Cloacal exstrophy

Cloacal exstrophy is a rare congenital disorder: a 2:1 male preponderance has been observed. 46 XY infant born with cloacal exstrophy are not usually considered to have a disorder of sex

Table 2
Categorisation of conditions presenting as XY females (46,XY DSD).

Group of condition	Clinical syndrome	Gene
Abnormalities of gonadal development	Gonadal dysgenesis – Swyer's syndrome	SRY, DHH, NR5A1
	Denys-Drash syndrome	WT1
	Campomelic dysplasia	SOX9
	Testicular regression syndrome	
Defects of testosterone synthesis	Leydig cell hypoplasia – LH receptor defects	LHGCR
	Steroidogenic enzyme deficiency	
	Lipoid adrenal hyperplasia	STAR, CYP11A1
	3β hydroxysteroid dehydrogenase type II deficiency	HSD3B2
	17α-hydroxylase and 17,20 lyase deficiency	CYP17A1
	17β hydroxysteroid dehydrogenase deficiency	HSD17B3
	Altered steroidogenesis due to disrupted electron transfer	
	P450 oxidoreductase defect	POR
Defect of testosterone processing	5α-reductase type 2 deficiency	SRD5A2
Defects in androgen action	Compete androgen insensitivity syndrome (CAIS)	AR
	Partial androgen insensitivity syndrome (PAIS)	AR
Ovotesticular 46,XY DSD		

development as they are genetically male with histologically normal testes and normal response to antenatal androgens in utero. Traditionally a female gender assignment is decided because of better long-term outcome [10,11] but this strategy has been challenged [12].

3.4. Inguinal hernia

The inguinoscrotal descent of testis is androgen dependent and inguinal hernia, in particular when bilateral, is the commonest presentation of complete AIS (CAIS) in childhood [8]. Among our population of 93 CAIS women, 32 (34%) presented inguinal hernia at a median age of 1 year (range 1 month to 11 years). It is estimated that 0.8–2.4% of premenstrual girls with inguinal hernia have CAIS [9] which is sufficiently common to warrant a karyotype in all instances.

3.5. Virilisation at puberty

The next age group to consider are those presenting with virilisation when they reach puberty. The clinical presentation includes failure to develop female secondary sex characteristics, enlargement of the clitoris, deepening of the voice and excessive body here in a male pattern distribution. The origin of androgens is likely to be testicular with concomitant AMH secretion and an absent uterus. This presentation pattern is most typical of 5AR deficiency, 17β-HSD deficiency.

3.6. Primary amenorrhoea

46 XY females presenting with primary amenorrhoea vary in their age of first assessment. This group either makes no andro-

gen such as in 46,XY gonadal dysgenesis, or is completely resistant to the effect of androgens such as in complete androgen insensitivity syndrome. The former group is also oestrogen deficient and therefore present with pubertal delay. Women with CAIS usually have normal breast development and so the presentation may be a little later than those with gonadal dysgenesis. The assessment of the uterus in women with oestrogen deficiency presenting with primary amenorrhoea is particularly difficult with the ultrasound often reporting an absent uterus. Our experience is to delay making any conclusion regarding uterine development until at least 6 months of oestrogen priming have taken place.
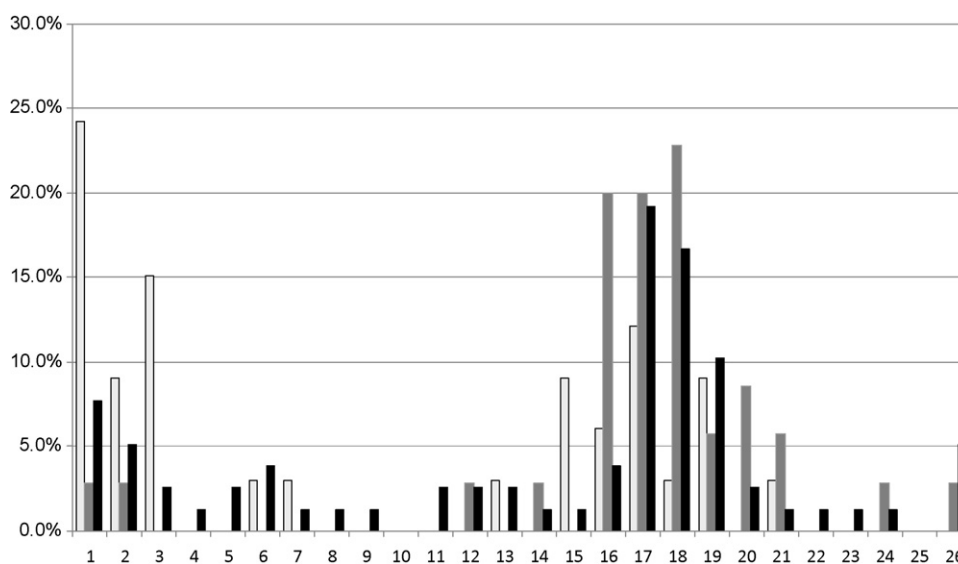
4. Diagnosis

Considerable progress has been made with understanding the genetic basis of human sexual development [13] yet a specific molecular diagnosis is identified in only in a small percentage of cases of DSD. Instead, most diagnoses are made in clinical grounds. From our experience the rate of inaccurate clinic diagnoses is high. Among a population of 46 XY females we discovered that only 47.8% have had accurate diagnosis [14]. This is especially true when we look at older patients who have had their diagnosis many years previously.

Ideally the diagnosis should be made at birth to assure the correct multidisciplinary assessment throughout childhood. It is well recognised that a delayed recognition of the condition can lead to grater difficulties in accepting the diagnosis [15–17]. For a correct diagnosis several aspects should be considered; Hormonal assays should be performed when gonads are in situ. It is much more difficult, if not impossible, to make an accurate diagnosis after gonadectomy. Access to specialist genetic and laboratory services

Table 3
UCLH DSD Clinic experience.

Condition	Numbers	Median (range) age	Median (range) age of diagnosis	Gonadectomy (%)	Median age of gonadectomy
CAIS	92	32.5 (16–64)	16 (0–25)	88%	17 (1–53)
PAIS	39	28.5 (17–66)	5.5 (0–31)	89%	12.5 (0–35)
GD	43	36 (17–59)	17 (0–53)	97%	18 (1–39)
Cloacal abnormalities	11	22 (13–30)	Birth	100%	<1 year
5ARD deficiency	8	29 (23–44)	15 (0–20)	100%	17 (3–27)
17β-HSD deficiency	7	26 (22–44)	11 (3–16)	57%	11.65 (3–16)
Mixed gonadal disgenesis	3	29 (25–35)	0.1 (0–1)	67%	1.5 (0–3)
STAR deficiency	2	30 (27–30)	16	100%	16
Denys-Drash syndrome	1	24			
Fraiser syndrome	1	28			
Leydig cell hypoplasia	1	37			
17 Hydroxylase deficiency	1	42			

Fig. 1. Frequency distribution of the age of presentation for the three largest diagnostic groups for which we had an accurate data. CAIS (*n* = 78, solid bars), PAIS (*n* = 33, shaded) Gonadal Disgenesis (*n* = 35, open).

leading to a genetic diagnosis should be made as efficient as possible.

The age of presentation varies according to the diagnostic category as shown from our clinic data (Fig. 1). For instance, for women with CAIS, the younger age groups for diagnosis comprise those who were found in utero and those who presented with inguinal hernias; there is then a second diagnostic group who present later with primary amenorrhoea. It is interesting that women with 46 XY gonadal dysgenesis commonly present years after the manifestation of delayed puberty which should be evident by the age of 16. For comparison, women presenting with ambiguous genitalia under the label of PAIS presents the earliest of these three groups.

Clinicians looking after adults with DSD will be familiar with the problem of meeting individuals for whom the diagnosis was made elsewhere many years previously. While a precise genetic diagnosis may not be critical to clinical management, lack of a clear diagnosis can often hamper discussions of the details of the condition. Strategies for making a diagnosis after gonadectomy are only now being developed. We have often found it helpful to retrieve as much clinical information as possible regarding early procedures in life in order to spend time going through each event and the details of each diagnostic procedure with women representing to clinic later in life. Lastly, information about clinical management and long-term health issues in adults are still scanty but the lack of evidence-based pathways should not be a barrier to effective care.

5. Psychological care

It is something of a paradox that although the discipline of Psychology has been profoundly implicated in the lives of people with DSD for half a century, psychological interventions targeting emotional and social adjustment in XY women can at best be described as embryonic. For some 50 years, psychologists in the field have mainly been academic researchers working within a neuroscience perspective. Academic interests in DSD has concentrated almost exclusively on their potential to help researchers determine the relative contributions of nature versus nurture to the gendered attributes and behaviours [18]. The way and extent to which this type of psychological research has benefited or harmed people with DSD will remain a contentious topic for debate.

Elsewhere, meanwhile, evidenced-based psychological interventions have been increasingly applied to advance quality care in modern health services. These are exciting developments that can also benefit patients with DSD. For XY woman, expert psychological input targeting emotional and social adjustment is as crucial as medical input. It is entirely possible for the women to live fully. However, some women may require emotional support and/or structured interventions to meet some of the following challenges: (1) explore thoughts and emotions about disclosure of aspects of DSD in a given social context; (2) manage the social stigma associated with the diagnosis and/or treatment(s) [19]; (3) weigh up any decision about having (more) genital surgery [20]; (4) overcome psychological barriers to initiate and maintain the dilation regime in order to maintain or create vaginal patency [21]; (5) clarify thoughts and feelings relating to sexuality, identity and relationships [22]; (6) manage sexual practice difficulties [13,23]; (7) confront the emotional challenges of infertility [22]; and (8) tackle communication barriers within the family, partnership and social network [24].

The existence of XY women undermines notions of sex dimorphism. Discussion contravenes social etiquette and the topic remains a taboo. In such a social context, full psychological adjustment on the patient's terms may not be a realistic goal at any one time. But a family's capacity for openness and growth will influence the developing child or adolescent or indeed adult. Thus psychological help should also be available to the family. It should go without saying that parents of children with DSD are offered expert psychological care early on, and to receive ongoing support as needs be.

Psychological approaches can also contribute to successful team development in clinical services, enabling clinicians to play to their strengths yet co-create innovative interdisciplinary care protocols for the benefit of patients and families, such as those that allow for smooth transitions. Furthermore, although there is evidence that DSD clinicians no longer practise concealment of diagnostic information [24], it can be surmised that that there is variability in physicians' and surgeons' levels of comfort and competence in relation to disclosure of difficult medical information. Responsible disclosure requires advance communication skills in the clinician, and psychologists can have an important role in providing training for colleagues, as well as in containing the emotional challenges that they face.

6. Genital surgery

Genital surgery in the XY woman falls into two categories:

- Feminising genital surgery
- Vaginal creation for a shortened or absent vagina

In conditions where the genitals are ambiguous at birth, feminising genital surgery is usually performed. Surgery consists of clitoral, vaginal and labial surgery to reduce the size of the prominent clitoris, to open the vaginal introitus, and achieve a more female appearance. This surgery is usually performed in the first year or so of life and has been standard practice for many years. Although the rationale behind such surgery has been challenged [25], the majority of adult women will have this type of reconstructive procedure as children. Long-term effects of such surgery include poor cosmetic appearance and vaginal stenosis. Revision surgery is very common in adolescent and adult life. Childhood reconstructive surgery can leave the genital area very scarred and unsuitable for vaginal dilation. Further major reconstructive surgery may be necessary and may require the use of an intestinal segment to create a neovagina. Recent work has also demonstrated that childhood clitoral surgery has a detrimental effect on sexual function in adult life [26]. Clitoral surgery has been shown to reduce the ability to orgasm, reduce sexual sensitivity and is detrimental to sexual satisfaction [27].

Women with CAIS have female external genitalia but may have a shortened vagina which requires treatment to allow penetrative intercourse. In this situation vaginal dilation treatment is usually effective. Dilation consists of pressing a cylindrical mould against the vaginal dimple for 30 min each day, until a vagina is created and can take 3–6 months to complete. Success levels are high in motivated patients and 85% of women should achieve a function vagina [28]. Despite the advantages of avoidance of surgery, dilation therapy can however be distressing with its reminders of abnormality [20] and psychological support is integral to the treatment. Where dilator therapy is not successful, the laparoscopic Vecchietti procedure provides an alternative [26]. This involves an acrylic olive being placed on the vaginal dimple, with threads being passed through the olive, up into the abdominal cavity, via laparoscopic guidance, and out onto the abdominal wall. The threads are then connected to a winch system, which "lifts" the vagina by 1 cm a day, Although successful in lengthening the vagina, this procedure does require a general anaesthetic and hospital stay. Dilator therapy, or regular sexual activity should be commenced after the vagina has been created, in order to retain the vaginal length.

7. Malignancies

XY female are more likely to develop gonadal tumours than normal female but, since adult XY women who did not have gonadectomy are rare, it is difficult to estimate the overall lifelong cancer risk.

The risk of malignancy is highest in women with 46XY gonadal dysgenesis with estimates of a life time risk between 12 and 35%. Women with PAIS with intra-abdominal gonads are also considered to be at high risk but the evidence base is for this data is limited [29–32]. In contrast, the risk of malignancy for women with ovotestis DSD and CAIS is estimated to be 2–3%.

Gonadectomy in the XY female is currently standard recommended medical practice because of the increased risk of malignancy and is usually performed laparoscopically [28]. The timing of surgery can vary according to diagnosis. If the diagnosis is of gonadal dysgenesis, gonadectomy should be performed soon after diagnosis because the malignancy risk is high and the gonads have no useful hormonal or reproductive function. In virilising conditions such as PAIS, 5AR deficiency or 17β-HSD deficiency, gonadectomy is best performed before puberty if the individual is raised female in order to prevent irreversible androgenisation [33]. In CAIS, the timing of gonadectomy is more controversial. Although past practice was to remove the gonads at diagnosis, it is more common now to leave the gonads in place until puberty is complete. The malignancy risk is low at this age and this allows spontaneous pubertal development without oestrogen replacement. It also allows the adolescent to be involved in the discussions around surgery. A small group of adult women chose to retain their gonads despite the malignancy risk. Some are reluctant to take hormone replacement and some are concerned about anecdotal reports of loss of energy and libido following gonadectomy. The testes in AIS are structurally normal and it is possible that fertility advances may mean these could be used in fertility treatment although the ethics of this are as yet unclear. The difficulty with retaining testes is the lack evidence that surveillance for malignancy is safe and effective. The testes are usually intra-abdominal and therefore impalpable. Neither ultrasound or magnetic resonance imaging can detect early invasive changes and tumour markers are not reliable. At present, gonadectomy soon after puberty is the safest option and patients wishing to retain their gonads must be aware of the associated risks of doing so.

8. Sex steroid replacement therapy

After gonadectomy, most women will require sex steroid replacement (hormone replacement therapy or HRT) continuously until approximately the age of 50. The principles of use of HRT for women with DSD is, for the most part the same and for any other women. The main treatment goals are to maintain a good quality of life, sexual function and optimal bone density. There are several options of treatment that include different routes of oestrogen administration and different progesterone formulations for those women with a uterus and consideration of testosterone supplements. Women without a uterus do not need to take progesterone.

The type of HRT is normally based on individual choice and the vast majority of women receive standard adult doses of oestradiol valerate 2 mg, conjugated equine oestrogens 0.625 mg, transdermal oestradiol 50 μg daily or oestradiol implant 50 mg every 6 months. Some young women prefer to use a combined oral contraceptive pill as a form of oestrogen as this is considered to be 'peer friendly' while others will find the suggestion of using 'the pill' absurd as they do not need contraception. The correct dose of oestrogen must be established based on quality of life and a trial of higher dose treatment is worthwhile for low energy or low libido. Vaginal oestrogen may be needed in addition to systemic oestrogen especially to facilitate vaginal dilation therapy or to improve vaginal lubrication.

Women without a uterus usually use unopposed oestrogens and in this situation an oestrogen implant is popular. For women with a uterus, progesterone must be used with choices including cyclical progesterone, continuous progesterone in combination with oestrogen or intrauterine progesterone as in the levonorgestrel intrauterine device.

Some issues relating to sex steroid replacement are particular to different forms of DSD.

Women with AIS are usually considered to have normal sex steroid levels prior to gonadectomy although there is some suggestion that they are relatively oestrogen deficient relying on the conversion from testosterone by aromatisation [34,35]. Nevertheless, pubertal development with respect to breast development is usually normal and HRT is needed only from the time of gonadectomy. There is a prominent anecdote that women with AIS have

greater vitality prior to gonadectomy when they are 'running on testosterone' compared to after gonadectomy when their sex steroid balance is based on oestrogen. Accepting that the reasons for this change in well being need not be solely hormone related, some women with AIS prefer to use testosterone replacement rather than oestrogen. Approximately 5% of women with AIS attending our clinic use testosterone such as testosterone esters 250 mg every 4 weeks by injection. Testosterone must be used cautiously in those who had a gonadectomy at a young age as the resistance to testosterone has not been firmly established in this group.

In complete gonadal dysgenesis the induction of puberty may have been delayed considerably depending on the timing of presentation. Oestrogen is introduced at a low dose and then increased gradually according to response. The pace of puberty is set on an individual basis according to the wishes of each individual. There is common notion that interval between starting oestrogen and introducing progesterone should be maximised for optimal uterine and breast development so it will often be in excess of 1 year before periods commence. Despite best efforts, breast hypoplasia can result from very delayed exposure to oestrogen and a proportion of women in this situation will consider breast augmentation surgery.

9. Bone

Several reports have shown a low bone density in women with AIS [36,37]. While there is some debate regarding the role of androgen resistance in contributing to low bone density, the only modifiable factor that is associated with bone integrity is compliance with HRT. That is, women with the lowest bone density have often gone through times of low oestrogen intake. The effect of oestrogen on bone is dose dependent and so we advise monitoring bone density at intervals and consider a higher dose of oestrogen in young women who do are not on target to achieve an adequate peak bone mass by the age of 35. In addition, for women who arrive at the age of 50 with low bone density then extended use of oestrogen may be considered.

In comparison to women with CAIS, those with 46XY GD have lower bone density presumably because of a greater degree of oestrogen deficiency prior to diagnosis [34]. We found that two thirds of women with 46XY DSD have osteopenia [38]. Early generous oestrogen replacement may allow for some catch up bone growth but whether a normal peak bone mass can be achieve for all women in this situation is not established.

For women with very low or deteriorating bone density, supplementary treatments such as vitamin D supplements and bisphosphonates are used according to conventional guidelines.

10. Fertility

Coordination of fertility options for women with DSD requires both knowledge of the potential for each individual but also of the provision of unusual fertility services. In the UK the three main choices for starting a family come under different agencies. Adoption comes under the auspices of social services, ovum donation is often provided by private fertility clinics and surrogacy is supported by a voluntary organizations (see internet resources).

Preparation for fertility may start with a clinical psychology assessment working through the plans and wishes of each individual. A fertility specialist is required to describe the practicalities of each option. Support groups are very helpful source of user information with forums passing on up to date experiences.

Women with no uterus will usually choose between surrogacy and adoption. Women with gonadal dysgenesis and a normal uterus may consider ovum donation. While ovum donation is available in the UK sometimes as part of the NHS fertility services, the rate-limiting step is the availability of donates oocytes. In order to circumvent any delay, many couples choose to enroll with clinics in Europe, India or North America were supplies of oocytes are less restricted. Successful pregnancies after egg donation in women with 46XY gonadal dysgenesis are still to few to be certain of success rates [39–42] Although rate of Caesarean Section may be increased [43], normal term vaginal delivery has been reported [39].

11. Conclusion

Women with a 46XY karyotype comprise a heterogeneous group who differ not only in their diagnostic category and anatomy but also in their journey through life to adult services. In individualised approach covering past experiences, current medical and surgical needs and future prospects is required for optimal care. A multidisciplinary team is helpful in providing this care and liaison with supports groups is essential in order to keep informed of current issues in this area. We conclude with a list of Internet recourses with that includes reference to the main support group in the UK; the AISSG.

Internet resources

AISSG Androgen Insensitivity Syndrome Support Group www.aissg.org.

COTS Childness Overcome Through Surrogacy www.surrogacy.org.uk.

Surrogacy UK www.surrogacyuk.org.

HFEA Human Fertilisation Embryology Authority www.hfea.gov.uk.

Daisy Network Premature Menopause Support Group www.daisynetwork.org.uk.

Contributors

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