Maturitas 65 (2010) 172–178

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Long-term health issues of women with XY karyotype

Marta Berra[a,b,*], Lih-Mei Liao[a,b], Sarah M. Creighton[a,b], Gerard S. Conway[a,b]

[a] Department of Adolescent Gynaecology and Reproductive Endocrinology, University College London Hospitals, UK
[b] Elizabeth Garrett Anderson UCL Institute for Women's Health, University College London, UK

ARTICLE INFO

Article history:
Received 27 November 2009
Accepted 3 December 2009

Keywords:
Disorder of sex development
Intersex
Gonadectomy
Psychological care

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.

Contents

1. Introduction 173
2. Definitions and terminology 173
3. Clinical presentations 173
   3.1. Diagnosis in utero 173
   3.2. Ambiguous genitalia at birth 173
   3.3. Cloacal exstrophy 173
   3.4. Inguinal hernia 174
   3.5. Virilisation at puberty 174
   3.6. Primary amenorrhoea 174
4. Diagnosis 174
5. Psychological care 175
6. Genital surgery 176
7. Malignancies 176
8. Sex steroid replacement therapy 176
9. Bone 177
10. Fertility 177
11. Conclusion 177
    Internet resources 177
    Contributors 177
    Provenance and peer review 177
    Conflict of interest 177
    References 177

* Corresponding author at: Department of Endocrinology, University College London Hospitals, 250 Euston Rd, London, NW112BU, UK.
Tel.: +44 (0)2073809101/+44 07742869694(mobile).
E-mail addresses: Marta.Berra@uclh.nhs.uk, martaber@gmail.com (M. Berra).

0378-5122/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.maturitas.2009.12.004

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 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.

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 Undervirilisated XY male	46,XY DSD
Female pseudohermaphrodite Masculinised of XX female	46,XX DSD
True hermaphrodite XX male, XX sex reversal	Ovotesticular DSD 46,XX testicular DSD

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