Asian Journal of Andrology (2017) 19, 168–172

www.asiaandro.com; www.ajandrology.com

Open Access

ORIGINAL ARTICLE

Male Fertility

46 XX karyotype during male fertility evaluation; case series and literature review

Ahmad Majzoub[1,2], Mohamed Arafa[3], Christopher Starks[4], Haitham Elbardisi[2], Sami Al Said[2], Edmund Sabanegh Jr[1]

Forty-six XX disorder of sex development is an uncommon medical condition observed at times during the evaluation of a man's fertility. The following is a case series and literature review of phenotypically normal men diagnosed with this karyotype. Our goal is to comprehend the patients' clinical presentation as well as their laboratory results aiming to explore options available for their management. A formal literature review through PubMed and MEDLINE databases was performed using "46 XX man" as a word search. A total of 55 patients, including those conveyed in this article were diagnosed with a 46 XX karyotype during their fertility evaluation. The patients' mean age ± s.d. was 34 ± 10 years and their mean height ± s.d. was 166 ± 6.5 cm. Overall, they presented with hypergonadotropic hypogonadism. Sexual dysfunction, reduced hair distribution, and gynecomastia were reported in 20% (4/20), 25.8% (8/31), and 42% (13/31) of the patients, respectively. The *SRY* gene was detected in 36 (83.7%) and was absent in the remaining seven (16.3%) patients. We found that a multidisciplinary approach to management is preferred in 46 XX patients. Screening for remnants of the mullerian ducts and for malignant transformation in dysgenetic gonads is imperative. Hypogonadism should be addressed, while fertility options are *in vitro* fertilization with donor sperm or adoption.

Asian Journal of Andrology (2017) **19**, 168–172; doi: 10.4103/1008-682X.181224; published online: 10 June 2016

Keywords: hypogonadism; infertility; male; sex-determining region; XX disorders of sex development

INTRODUCTION

Infertility is a common medical problem affecting roughly one out of six couples.[1] A male factor is either responsible for or contributory to about half the cases.[2] Once conception fails to occur after at least 12 months of regular unprotected intercourse, the couple's fertility is often investigated. Genetic testing in men has a distinctive set of indications that are usually picked up during the initial workup. Marked reduction of sperm concentration, unilateral/bilateral absence of vas deference, and suggestive family history are influential factors. Chromosomal abnormalities occur in <1% of the general population,[3] however their incidence rises up to 15% in men with infertility.[4]

The 46 XX testicular disorder of sex development (DSD), previously known as *de la Chapelle* syndrome after its first report in 1964,[5] comprises a small share of genetic causes of male infertility. It is a rare condition occurring in about 1:20 000 males[6] and characterized by a variable degree of mismatch between the phenotype and the genotype of the affected individual. Patients may present seeking fertility with normal male internal and external genitalia, or may present at an earlier age because of ambiguous genitalia. Undescended testes, micropenis, and hypospadias are commonly reported,[7] as well as residual remnants of the mullerian tract.[8] What preserves a male phenotype in these individuals is translocation of the sex-determining region Y gene (*SRY*) into a sex chromosome or an autosome, a process occurring in about 80% of cases.[9] In the remaining *SRY*-negative patients, presumed hidden mosaicism for the *SRY* gene or possible mutation of inhibitors of the male pattern has been postulated.[9]

In this study, we report a series of cases of 46 XX men presenting with infertility and perform a formal literature review of similar cases aiming to provide a comprehensive approach for managing this relatively rare condition.

PATIENTS AND METHODS

We reviewed the records of patients presenting for initial male fertility evaluations during the period from 2011 to 2015 at two institutions (Cleveland Clinic and Hamad Medical Center). We identified six patients who were found, with genetic testing, to have 46 XX karyotype. The patients' medical records were checked for information regarding their presentation, significant medical problems, biologic data, physical examination, and laboratory investigations.

Semen analysis

All patients were evaluated with semen analysis and hormonal profile. The semen analysis was performed after 3–5 days of sexual abstinence. Collection is done through masturbation into a clean container. Samples were incubated at 37°C and allowed to liquefy for 30 min before analysis. The analysis was performed according to the WHO guidelines adopted in 2010.[10]

Hormone profile

Hormones investigated constituted of follicular stimulating hormone (FSH) (normal level [nl]: 1–9 IU l^{-1}), luteinizing hormone (LH)

[1]Cleveland Clinic Foundation, Department of Urology, Cleveland, Ohio, USA; [2]Hamad Medical Corporation, Department of Urology, Qatar; [3]Cairo University, Department of Andrology, Giza, Egypt; [4]Reston Hospital, Department of Urology, Virginia, USA.
Correspondence: Dr. A Majzoub (dr.amajzoub@gmail.com)
Received: 16 November 2015; Revised: 21 January 2016; Accepted: 10 March 2016

(nl: 1–9 IU l^{-1}), prolactin (nl: 2–14 ng ml^{-1}), total testosterone (nl: 220–1000 ng dl^{-1}), and estradiol (nl: 10–60 pg ml^{-1}).

Cytogenetic and FISH investigations

Genetic testing in the form of karyotype and Y chromosome micro-deletion analysis was performed on all patients according to practice guidelines. A conventional chromosome analysis was performed from patients' peripheral blood lymphocytes, which were cultured in RPMI 1640 medium, phytohemagglutinin, and fetal bovine serum for 72 h, followed by treatment with 50 μg ml^{-1} colcemid. Metaphase chromosome spreads were studied by standard GTG and CBG banding procedures, which included using trypsin and Giemsa for G-banding and barium hydroxide for C-banding. FISH was performed on thirty metaphase chromosome spreads using a mixture of probes specific for DXZ1 and DYZ3, and a chromosome-specific probe for CBFB GLP 16 banding at 16q22. Multiplex PCR amplification of nine sequence-tagged site markers was used to detect AZF region micro-deletions on the Y chromosome.

Literature review

A formal literature review was performed using PubMed and MEDLINE databases for the period from 1964 to 2015. The search word "46 XX man" was used. Search results were reviewed for relevance and quality. The inclusion criteria were studies reporting adult patients presenting with infertility and in English language. Case reports of patients of pediatric age group as well as those investigated for reasons other than infertility were excluded. The Institutes' Ethics Committee accepted the research, and a waiver of signed informed consent was used.

RESULTS

Six patients were found to have 46 XX karyotype and were included in this study. The patients' mean age ± s.d. was 34.3 ± 4.5 years. A normal male phonotype was detected in all except one patient who had a eunuchoid habitus characterized by increased fat distribution, reduced virilization, and gynecomastia. The patients' mean testicular volume ± s.d. was 5.5 ± 1.8 ml. All patients presented with primary infertility and had normal volume azoospermia on semen analysis. Hormone analysis revealed hypergonadotropic hypogonadism with a mean testosterone, FSH, and LH ± s.d. of 158.8 ± 107 ng dl^{-1}, 22.2 ± 11.2 IU l^{-1}, and 14.2 ± 5.7 IU l^{-1}, respectively. FISH confirmed the presence of a translocated SRY region on the long arm of the X chromosome in five patients and its absence in the sixth patient. Other characteristics of their presentation are shown in **Table 1**.

The literature search resulted in 152 articles. After meticulous review, 29 papers met the inclusion criteria and contained 49 patients with 46 XX DSD. **Table 1** displays all literature cases, including those reported in this study, of 46 XX men diagnosed during fertility evaluation. The reported mean age ± s.d. was 34 ± 10 years. Sexual dysfunction, reduced hair distribution, and gynecomastia were reported in 21% (4/19), 26.6% (8/30), and 40% (12/30) of patients, respectively. Patients' mean height ± s.d. was 166 ± 6.5 cm. Overall, patients had hypergonadotropic hypogonadism with a mean testosterone ± s.d. of 274.3 ± 135.3 ng dl^{-1}, mean FSH ± s.d. of 40.4 ± 22.2, and mean LH ± s.d. of 23.4 ± 13.4. FISH was performed in 43 patients. The *SRY* gene was detected in 36 (83.7%) and was absent in the remaining 7 (16.3%) patients. The translocation was to a sex chromosome in 95% (38/40) and to an autosome in 5% (2/40) of the patients. In two out of the seven *SRY*-negative patients, the authors investigated the *DAX1* and *SOX9* genes and failed to detect any mutation. Testicular atrophy was reported in all cases while testis biopsy was performed in ten patients and showed absence of spermatogenesis with Sertoli cell only and Leydig cell hyperplasia.

DISCUSSION

46 XX DSD is a genetic abnormality infrequently encountered by andrologists during fertility evaluation of phenotypically normal males. Once encountered, a thorough understanding of all its implications is mandatory for adequate management and counseling. Several etiologic theories have been proposed to help understand this condition. In *SRY*-positive patients, cross-over between pseudoautosomal regions of sex chromosomes is believed to occur during paternal meiosis.[11] Whereas in *SRY*-negative patients, the link remains unclear. Some have advocated the presence of different sex determining genes located on autosomes initiating "maleness."[12] For example, *SOX9* gene, which is located on the long arm of chromosome 17, is known to potentiate *SRY* gene effects and its overexpression has been linked to 46 XX *SRY*-negative males.[13] Others believe that the SRY gene is in fact inhibitory to other autosomal genes, termed "Z" genes, that are themselves inhibitory to male sex determination.[14] Furthermore, an X-linked dosage-sensitive sex reversal locus has been identified and functions as a repressor of male pathway. Meeks *et al.* confirmed that mutations to the *DAX1* gene would lead to 46 XX female-to-male sex reversal.[15] Of all the cases of 46 XX DSD reported in men seeking fertility, the *SRY* gene was present in 83.7% and absent in 16.3%. Two cases performed PCR amplification of the SOX9 and DAX1 regions and failed to find any mutation. Unfortunately, these mutations were also not assessed in our *SRY*-negative patient.

A number of characteristic features are picked up during physical examination but are not sufficient to make a diagnosis. Unlike Klinefelter patients (47 XXY) who can present with similar complaints, patients with 46 XX DSD generally have a short stature which is mainly due to lack of testosterone-driven pubertal growth spurt or due to absence of other Y-chromosome specific growth factors.[16] The mean height ± s.d. of reported cases in this review was 166 ± 6.5 cm. The degree of virilization is variable. While it is complete in some patients, others may have poor hair growth, female fat distribution, and gynecomastia secondary to an altered testosterone/estradiol ratio. This imbalance is thought to result from an increase in peripheral aromatization of testosterone. A finding that is influenced by the increase in fat mass and the decrease in lean muscle mass, which is often seen in many chromosomal disturbances with subsequent hypogonadism.[17] This variability can be explained by the hypogonadism often in existent or may be secondary to a dose-dependent genetic aberration, as has been postulated by some researchers.[18] Up to 40% of cases had some form of reduced virilization.

Testicular atrophy is always detected on genital examination, in addition to other less frequent abnormalities such as undescended testis and hypospadias,[19] which have been reported in 5.5% and 7.4% of cases in this review.

Azoospermia is present on semen analysis as would be expected since all Y chromosome azoospermia factors (AZF) are lacking.[20] Serum hormone testing reveals hypergonadotropic hypogonadism consistent with primary testicular failure. The mean ± s.d. of serum testosterone, FSH, and LH reported in all cases were 274.3 ± 135.3 ng dl^{-1}, 40.4 ± 22.2 IU ml^{-1}, and 23.4 ± 13.4 IU ml^{-1}, respectively. Once karyotype analysis fails to detect a Y chromosome in a phenotypic male, FISH or molecular amplification by polymerase chain reaction (PCR) is performed to look for the presence or absence of *SRY* gene. Although this workup does not have a prognostic value, it documents the various genetic rearrangements of the syndrome.

Table 1: 46 XX DSD men presenting with infertility

References	*Case*	*Clinical data*								*Hormones*					*Genetics*		*Pathology histology*
		Age (years)	*ED*	*Reduced HD*	*GM*	*Penis size (cm)*	*Other*	*Weight (kg)*	*Height (cm)*	*T (ng dl^{-1})*	*FSH (IU l^{-1})*	*LH (IU l^{-1})*	*E (pg ml^{-1})*	*PRL (ng ml^{-1})*	*SRY*	*Location**	
Rigola *et al*. 2002[34]	1	33		No	No	NL									+	Xp	
Valetto *et al*. 2005[35]	2	35		No	No	NL		48	152	306	23.9	17.7		7.13	–		
Dauwerse, *et al*. 2006[11]	3	61			No	NL	SS		171	325.4	13	10	31.3		+	16q	
Kim, *et al*. 2015[33]	4	29	Yes	No	No	10.7^		62	165	179	76	41			–		Hyalinization, LCH
Ryan *et al*. 2013[18]	5	40	No	Yes	No	3.6[e]					1		10		–		
Gao *et al*. 2013[36]	6								163	308.7	93.6	19.4	33	17.9	+	Xp	
	7								163	277.6	24.7	14.4	43	18.5	+	Xp	
	8								162	129.6					+	Xp	
	9								161	137.6	81.6	27.7	19.8	22.9	+	Xp	
	10								158	244.5	13.1	3.61	34	9.67	+	Xp	
	11								162	172.8	54.7	19.4	27	10.08	+	Xp	
	12								162	319.6	37.1	16.5	28	9.88	+	Xp	
	13								161	216	43	33.9	22	7.28	+	Xp	
	14								160	336.9	72	34.6	19.8	10	+	Xp	
	15								160	180.8	49	26.8	19.8	15.8	+	Xp	
	16								161	521.2	87.7	31.4	30.5	49.6	+	Xp	
Xiao *et al*. 2013[37]	17	27	No		No	NL	HS		170	180	47	18.7	12	14.6	–	**	
Rizvi 2008[21]	18	33	No			8.6[e]		85.8	177	207	46	23			+	Xp	
Minor *et al*. 2008[38]	19	24			Yes					11.9[♯]	55.4	28.4			+	Xp	
Rajender Thangaraj, *et al*. 2006[9]	20	34		No	No	NL		64	156	580	25.8	15.8			–	**	
Queralt *et al*. 2008[39]	21	31		No	No			58	170	323	62.2	25.8	17		+	1q	
Tan *et al*. 1993[8]	22	32	No	No	Yes	Small	HS		176	263.2	21	34	25				
Zakharia *et al*. 1990[12]	23	28	No		Yes	NL		65	165	240	72	61		16.3			Leydig and Sertoli cell hyperplasia
Chiang *et al*. 2013[40]	24	33	No							203	46.5	17.6		27.05	+	Xp	
	25	34					UT			217	54.3	19.6		8.15	+	Xp	
	26	52					HS			144	64.3	20.2		16.08	–		
Wu *et al*. 2014[41]	27								165	195.8	35.5	13.8	30.5	4.6	+	Xp	
	28								162	155.5	29.2	12.9	19.1	3.6	+	Xp	
	29								164	256.3	45.9	25.1	26.7	7.8	+	Xp	
	30								167	241.9	33.7	22.3	29.1	10.9	+	Xp	
	31								165	201.6	31.4	19.6	22.1	7.8	+	Xp	
Tomomasa, *et al*. 1999[25]	32	25		No	No			55	177	428.6	19.7	10.3			+	Xp	Hyalinization, SCO
Jain, *et al*. 2013[26]	33	38	Yes	No	Yes	NL		63	162	120	76.6	36.3			+	Xp	FNA: SCO
Chernykh *et al*. 2009[42]	34	37		Yes	Yes			74	160	290.8	26.9	13.5			+	Xp	
Yencilek *et al*. 2005[27]	35	26	No	No	No	8[e]		72	165	270	45.6	48.9		9.4			LCH and tubule sclerosis
Butler, *et al*.1983[28]	36	31	No	No	Yes	7[e]		72	169	477	51				+		Tubular atrophy, absent spermatogenesis, LCH
Castineyra *et al*. 2002[43]	37	28		No	Yes				180	300	50	16	28	14	+	Xp	
	38	35		No			SS, UT		170	700	3.5	6.2	38	3.4	+	Xp	
	39	28		Yes			HS		160	140	21	5.2	19	8.1	+	Xp	
	40	39		Yes					174	560	6.7	4.2	30	6.2	+	Xp	
	41	24		No					172	300	45	40	20	5.4	+	Xp	
Fuse, *et al*. 1991[29]	42	30		No	No			90	172	160	47	60			+	Xp	Germinal aplasia, LCH
Pais *et al*. 1977[30]	43	29	No	No	Yes	Small		82	170	267	53	45					Hyalinization, SCO, LCH
Wegner *et al*. 1983[31]	44	35		No	No	NL		81	167	630	23.7	37.1		3.8	+	Xp	SCO, LCH
Micic *et al*. 1983[32]	45	25	No	Yes	No			63	171	319.6	31	18	47	6.8			SCO, LCH

Contd...

Table 1: Contd...

References	*Case*	*Clinical data*								*Hormones*					*Genetics*		*Pathology histology*
		Age (years)	*ED*	*Reduced HD*	*GM*	*Penis size (cm)*	*Other*	*Weight (kg)*	*Height (cm)*	*T (ng dl^{-1})*	*FSH (IU l^{-1})*	*LH (IU l^{-1})*	*E (pg ml^{-1})*	*PRL (ng ml^{-1})*	*SRY*	*Location**	
Matthews *et al*. 1983[44]	46	27		Yes	No		UT, FFD	68	166	282.2	46	19	33	9.87			
Pepene *et al*. 2008[45]	47	28	No	No	Yes		FFD	65	167	333.2	43.9	25.3			+	Xp	
Hado *et al*. 2003[46]	48	76	No	No	Yes				157	259	27.8	21			+	Xp	
Mustafa *et al*. 2010[47]	49	30		No	Yes	NL		75	170	211		40.7	16.6	8.5	–		
Current study	50	40	No	No	No	NL		84	175	335	38	12	29	13.6	+	Xp	
	51	31	No	No	No	NL				129	14	6	25	3.2	+	Xp	
	52	35	Yes	Yes	Yes	NL				74	10	23	5.7		+	Xp	
	53	29	No	No	No	NL		77	181	246	13.4	12	19		+	Xp	
	54	39	No	No	No	NL	SS	74	160	74	28	15			–		
	55	32	No	No	Yes	NL		86	170	95	29.7	16.9		12	+	Xp	

*Methods used for detection of SRY were fluorescence *in situ* hybridization, polymerase chain reaction, DNA hybridization, and high resolution banding; ^Erect length; ᵠFlaccid length; ♂Free testosterone (pg ml^{-1}); ***DAX1* and *SOX9* genes amplified and reported as normal. ED: erectile dysfunction; HD: hair distribution; T: testosterone; LH: luteinizing hormone; FSH: follicular stimulating hormone; E: estradiol; PRL: prolactin; *SRY*: sex determining region Y gene; SS: hypoplastic scrotum; HS: hypospadias; UT: undescended testis; FFD: female fat distribution; LCH: leydig cell hyperplasia; GM: gynecomastia; DSD: disorder of sex development; NL: normal level

SRY-negative patients are believed to have a higher frequency of genital ambiguities,[21] this particular association was not found in this subset of 46 XX DSD patients.

A multidisciplinary approach to management is favored after reaching the diagnosis. Genetic counseling is required to help the patient and his partner understand various aspects of his condition, in addition to psychological support, which would ease his comprehension of difficult information. Imaging of the pelvis is required to look for remnants of mullerian ducts that may cause morbidity in the form of repeated infections or urinary incontinence[22] and require surgical removal. Neoplastic transformation (gonadoblastoma) of dysgenetic gonads has been described in up to 30% of cases specifically when Y chromosome material is detected.[23] As such, serial self-examinations should be encouraged together with regular gonadal ultrasound imaging. Repeated gonadal biopsy and even gonadectomy in nonfunctioning gonads have also been proposed to overcome the risk of malignancy.[24] Testicular biopsy has been reported in ten cases displaying unified absence of germinal cells and Leydig cell hyperplasia.[12,25–33] Surgical correction of genital ambiguities such as hypospadias and undescended testis is required. Cosmetic surgery for gynecomastia should also be considered if the patient desires.

The patient's hypogonadism should be managed with testosterone replacement. Therefore, discussion about different forms of testosterone therapy and their possible side effects should be considered early after diagnosis. Prior to initiating therapy, a baseline bone density scan (DEXA) should be performed to look for osteopenia or frank osteoporosis. Patients with a T score of <−1.0 would benefit from treatment with Vitamin D and calcium, bisphosphonates, or calcitonin, and require annual repeats of DEXA scan until results are normal.[19] As regards to fertility, options are limited to artificial insemination or *in vitro* fertilization using donor sperm or resolving to adoption.

CONCLUSION

46 XX DSD is a rare genetic disorder that is seldom picked up during evaluation of patients with infertility. An understanding of all aspects of this condition is certainly required for offering the most suitable treatment. Herein, we report the largest single report case experience as well as the largest review of worldwide experience with 46 XX DSD detected during fertility evaluation.

AUTHOR CONTRIBUTIONS

AM participated in the acquisition of data, summarized the collected evidence, and drafted the manuscript. MA designed the study and participated in the acquisition of data. SC participated in the acquisition of data. HA revised the manuscript and helped in coordination. SA revised the manuscript and helped in co-ordination. ES helped to draft the manuscript and provided supervision. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

REFERENCES

1 Irvine DS. Epidemiology and aetiology of male infertility. *Hum Reprod* 1998; 13 Suppl 1: 33–44.
2 Thonneau P, Marchand S, Tallec A, Ferial ML, Ducot B, *et al*. Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988-1989). *Hum Reprod* 1991; 6: 811–6.
3 Lilian YF. Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In: Aubrey Milunsky, editor. Genetic Disorders of the Fetus. Baltimore, London: The Johns Hopkins University Press; 1998. p. 179–248.
4 Shi Q, Martin RH. Aneuploidy in human sperm: a review of the frequency and distribution of aneuploidy, effects of donor age and lifestyle factors. *Cytogenet Cell Genet* 2000; 90: 219–26.
5 de la Chapelle A, Hortling H, Niemi M, Wennstroem J. XX sex chromosomes in a human male. First case. *Acta Med Scand* 1964; 175 Suppl 412: 25–8.
6 de la Chapelle A. Etiology of maleness in XX men. *Hum Genet* 1981; 58: 105.
7 Vorona E, Zitzmann M, Gromoll J, Schuring AN, Nieschlag E. Clinical, endocrinological, and epigenetic features of the 46, XX male syndrome, compared with 47, XXY Klinefelter patients. *J Clin Endocrinol Metab* 2007; 92: 3458–65.
8 Tan TT, Khalid BA. Primary infertility in a phenotypic male with 46XX chromosomal constitution. *Postgrad Med J* 1983; 69: 315–7.
9 Rajender S, Rajani V, Gupta NJ, Chakravarty B, Singh L, *et al*. SRY-negative 46, XX male with normal genitals, complete masculinization and infertility. *Mol Hum Reprod* 2006; 12: 341–6.
10 Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, *et al*. World Health Organization reference values for human semen characteristics. *Hum Reprod Update* 2010; 16: 231–45.
11 Dauwerse JG, Hansson KB, Brouwers AA, Peters DJ, Breuning MH. An XX male with the sex-determining region Y gene inserted in the long arm of chromosome 16. *Fertil Steril* 2006; 86: 463.e1–5.
12 Zakharia G, Krauss DJ. Sex reversal syndrome (XX male). *Urology* 1990; 36: 322–4.
13 Kojima Y, Hayashi Y, Mizuno K, Sasaki S, Fukui Y, *et al*. Up-regulation of SOX9 in human sex-determining region on the Y chromosome (SRY)-negative XX males. *Clin Endocrinol (Oxf)* 2008; 68: 791–9.
14 McElreavey K, Vilain E, Abbas N, Herskowitz I, Fellous M. A regulatory cascade hypothesis for mammalian sex determination: SRY represses a negative regulator of male development. *Proc Natl Acad Sci U S A* 1993; 90: 3368–72.

15 Meeks JJ, Weiss J, Jameson JL. Dax1 is required for testis determination. *Nat Genet* 2003; 34: 32–3.
16 Ogata T, Hawkins JR, Taylor A, Matsuo N, Hata J, *et al*. Sex reversal in a child with a 46, X, Yp+karyotype: support for the existence of a gene(s), located in distal Xp, involved in testis formation. *J Med Genet* 1992; 29: 226–30.
17 Aksglaede L, Molgaard C, Skakkebaek NE, Juul A. Normal bone mineral content but unfavourable muscle/fat ratio in Klinefelter syndrome. *Arch Dis Child* 2008; 93: 30–4.
18 Ryan NA, Akbar S. A case report of an incidental finding of a 46, XX, SRY-negative male with masculine phenotype during standard fertility workup with review of the literature and proposed immediate and long-term management guidance. *Fertil Steril* 2013; 99: 1273–6.
19 Boucekkine C, Toublanc JE, Abbas N, Chaabouni S, Ouahid S, *et al*. Clinical and anatomical spectrum in XX sex reversed patients. Relationship to the presence of Y specific DNA-sequences. *Clin Endocrinol (Oxf)* 1994; 40: 733–42.
20 Vogt PH, Edelmann A, Kirsch S, Henegariu O, Hirschmann P, *et al*. Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. *Hum Mol Genet* 1996; 5: 933–43.
21 Rizvi AA. 46, XX man with SRY gene translocation: cytogenetic characteristics, clinical features and management. *Am J Med Sci* 2008; 335: 307–9.
22 Morgan RJ, Williams DI, Pryor JP. Mullerian duct remnants in the male. *Br J Urol* 1979; 51: 488–92.
23 Manuel M, Katayama PK, Jones HW Jr. The age of occurrence of gonadal tumors in intersex patients with a Y chromosome. *Am J Obstet Gynecol* 1976; 124: 293–300.
24 Tekgul S, Dogan HS, Erdem E, Hoebeke P, Kocvara R, *et al*. European Society for Paediatric Urology Guidelines on Pediatric Urology. European Association of Urology. http://uroweb.org/wp-content/uploads/22-Paediatric-Urology_LR.pdf; 2015. [Last accessed on 2016 Apr 2].
25 Tomomasa H, Adachi Y, Iwabuchi M, Tohyama Y, Yotsukura M, *et al*. XX-male syndrome bearing the sex-determining region Y. *Arch Androl* 1999; 42: 89–96.
26 Jain M, Veeramohan V, Chaudhary I, Halder A. The Sertoli cell only syndrome and glaucoma in a sex – Determining region Y (SRY) positive XX infertile male. *J Clin Diagn Res* 2013; 7: 1457–9.
27 Yencilek F, Baykal C. 46×X male syndrome: a case report. *Clin Exp Obstet Gynecol* 2005; 32: 263–4.
28 Butler MG, Walzak MP, Sanger WG, Todd CT. A possible etiology of the infertile 46XX male subject. *J Urol* 1983; 130: 154–6.
29 Fuse H, Satomi S, Kazama T, Katayama T, Nagabuchi S, *et al*. DNA hybridization study using Y-specific probes in an XX-male. *Andrologia* 1991; 23: 237–9.
30 Pais VM, Vasudevan P. Infertility in an XX male. *J Urol* 1977; 118: 690–1.
31 Wegner RD, Nurnberger F. Clinical, cytological, and biochemical investigations in a case of an XX male. *Andrologia* 1983; 15: 253–8.
32 Micic S, Micic M, Ozerovic B. An example of a 46, XX infertile man and his permanent tooth sizes. *Int J Fertil* 1983; 28: 165–8.
33 Kim MS, Hwang PH, Lee DY. A 46, XX male adolescent presenting with a chief complaint of gynecomastia. *Pediatr Neonatol* 2015; 56: 357–9.
34 Rigola MA, Carrera M, Ribas I, Egozcue J, Miro R, *et al*. A comparative genomic hybridization study in a 46, XX male. *Fertil Steril* 2002; 78: 186–8.
35 Valetto A, Bertini V, Rapalini E, Simi P. A 46, XX SRY-negative man with complete virilization and infertility as the main anomaly. *Fertil Steril* 2005; 83: 216–9.
36 Gao X, Chen G, Huang J, Bai Q, Zhao N, *et al*. Clinical, cytogenetic, and molecular analysis with 46, XX male sex reversal syndrome: case reports. *J Assist Reprod Genet* 2013; 30: 431–5.
37 Xiao B, Ji X, Xing Y, Chen YW, Tao J. A rare case of 46, XX SRY-negative male with approximately 74-kb duplication in a region upstream of SOX9. *Eur J Med Genet* 2013; 56: 695–8.
38 Minor A, Mohammed F, Farouk A, Hatakeyama C, Johnson K, *et al*. Genetic characterization of two 46, XX males without gonadal ambiguities. *J Assist Reprod Genet* 2008; 25: 547–52.
39 Queralt R, Madrigal I, Vallecillos MA, Morales C, Ballesca JL, *et al*. Atypical XX male with the SRY gene located at the long arm of chromosome 1 and a 1qter microdeletion. *Am J Med Genet A* 2008; 146A: 1335–40.
40 Chiang HS, Wu YN, Wu CC, Hwang JL. Cytogenic and molecular analyses of 46, XX male syndrome with clinical comparison to other groups with testicular azoospermia of genetic origin. *J Formos Med Assoc* 2013; 112: 72–8.
41 Wu QY, Li N, Li WW, Li TF, Zhang C, *et al*. Clinical, molecular and cytogenetic analysis of 46, XX testicular disorder of sex development with SRY-positive. *BMC Urol* 2014; 14: 70.
42 Chernykh VB, Kurilo LF, Shilova NV, Zolotukhina TV, Ryzhkova OP, *et al*. Hidden X chromosomal mosaicism in a 46, XX male. *Sex Dev* 2009; 3: 183–7.
43 Castineyra G, Copelli S, Levalle O. 46, XX male: clinical, hormonal/genetic findings. *Arch Androl* 2002; 48: 251–7.
44 Matthews CD, Ford J, Kirby C. The XX male. Clinical and theoretical aspects. *Clin Reprod Fertil* 1983; 2: 207–15.
45 Pepene CE, Coman I, Mihu D, Militaru M, Duncea I. Infertility in a new 46, XX male with positive SRY confirmed by fluorescence *in situ* hybridization: a case report. *Clin Exp Obstet Gynecol* 2008; 35: 299–300.
46 Hado HS, Helmy SW, Klemm K, Miller P, Elhadd TA. XX male: a rare cause of short stature, infertility, gynaecomastia and carcinoma of the breast. *Int J Clin Pract* 2003; 57: 844–5.
47 Mustafa O, Mehmet E. A 46, XX SRY – Negative man with infertility, and co-existing with chronic autoimmune thyroiditis. *Gynecol Endocrinol* 2010; 26: 413–5.