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## Fertility in men with Klinefelter's syndrome

### Fertilité et syndrome de Klinefelter

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#### ABSTRACT

Patients with a Klinefelter syndrome (KS), defined by a 47 XXY karyotype, were long considered infertile. Testicular sperm extraction (TESE) now allows them to access fatherhood. We will present the data of studies since first experiment of TESE. Several factors influencing TESE outcome were proposed in these different studies. Among them, clinical and hormonal parameters have reported by few studies, age has been one of the most discussed prognostic factor of positive sperm retrieval rate. Data seems to show that TESE carried out before an age greater than 30 has a poorer prognosis for positive sperm retrieval. In few studies performed in younger patient, before 20 years, SRR was closed to result for 20 to 30 year old patients. Offering a TESE before 16 years old does not improve positive sperm extraction rate. In fact, the few studies carried out before the age of 16 were of poorer prognosis, most often linked to insufficient maturation of the residual gametes. In addition, androgen therapy, frequently prescribed in case of Klinefelter syndrome, did not seem to show any effect on sperm retrieval but only few studies were interested in the possible impact of this treatment. In conclusion, further studies are necessary to determine the interest of new markers to predict the chance of sperm retrieval, taking into account age, hormonal therapy.

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#### RÉSUMÉ

Les patients atteints d'un syndrome de Klinefelter (SK), défini par un caryotype 47 XXY, ont longtemps été considérés comme infertiles. L'extraction de sperme testiculaire (TESE) leur permet désormais d'accéder à la paternité. Nous présenterons les données d'études depuis la première expérimentation de TESE. Plusieurs facteurs influençant le résultat du TESE ont été proposés dans ces différentes études. Parmi eux, les paramètres cliniques et hormonaux ont été cités par certains, l'âge a été l'un des facteurs pronostiques les plus discutés pouvant être corrélé au taux de récupération de sperme. Les données semblent montrer que le TESE effectué avant un âge supérieur à 30 ans serait de moins bon pronostic pour une extraction positive du sperme. Dans quelques études réalisées chez des patients plus jeunes, avant 20 ans, le résultat

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d'extraction des spermatozoïdes était proche de ceux pour les patients âgés de 20 à 30 ans. Proposer un TESE avant 16 ans n'améliore pas le seuil de positivité d'extraction des spermatozoïdes. En effet, les quelques études réalisées avant 16 ans étaient de moins bon pronostic, le plus souvent lié à une maturation insuffisante des gamètes résiduels. De plus, l'androgénothérapie, fréquemment prescrite en cas de syndrome de Klinefelter, ne semble pas montrer d'effet sur la récupération des spermatozoïdes testiculaires mais seules quelques études se sont intéressées à l'impact éventuel de ce traitement. En conclusion, d'autres études apparaissent utiles pour déterminer l'intérêt de nouveaux marqueurs pour prédire les chances de prélèvement de sperme, prenant en compte l'âge, l'hormonothérapie.

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## 1. Introduction

Klinefelter syndrome (KS) prevalence is estimated at 1/500 to 1/700 newborn males. In 1942, H.F. Klinefelter et al. [1] described this syndrome characterized by gynecomastia, small and firm testes, azoospermia and elevation of serum FSH with functional Leydig cells. In 1959, P.A. Jacobs and J.A. Strong suggested the presence of an extra X chromosome to be the cause for the syndrome [2]: Classical karyotype is 47, XXY. About 80% of Klinefelter syndromes are due to the congenital numerical chromosome aberration 47, XXY; the remaining 20% are cases with mosaicisms or with lineage carrying more extra X chromosomes and at least one Y chromosome (e.g. 47,XXY/46,XY, 47,XXY/45,X/46,XY, 48,XXX, 49,XXXXY, 48,XXYY, mosaicism, or structurally abnormal X chromosomes) [3]. These last ones are also considered as Klinefelter's syndrome variants, although the clinical presentation may be quite different in some cases [4].

This karyotype is observed in 11% of azoospermic patients and 1–2% of infertile men [3]. Around 10% of cases were identified prenatally and 26% in childhood or adult life and 64% remains undiagnosed [5].

After reviewing pathophysiology of the disorder of spermatogenesis in case of Klinefelter syndrome, we will focus of the possibilities of fertility and then prognosis factors.

## 2. Pathogenesis of spermatogenesis failure

Numerical chromosome aberrations occur during meiotic divisions in germ cell development or cell divisions in early embryonic development. Since the first description of KS, the molecular mechanism of the syndrome remains unknown. In different animal models and in humans, it has been described the presence of primordial germ cells in the fetal testis of XXY males but these germ cells degenerate during the childhood, disappear at the puberty and adulthood [6].

However, oligospermia has been observed in cases of 46XY/47,XXY mosaicism and histopathological studies have shown various aspect: meiosis arrest and foci of normal spermatogenesis in few seminiferous tubules [7–9].

Sciurano et al. [10] confirmed previous suggestion and confirmed that spermatogenic foci probably originate from clones of spermatogonia that have randomly loss of the X chromosome. The loss of one extra X occurs probably during spermatogonial mitotic activity of the fetal life.

## 3. Fertility in Klinefelter syndrome?

Until the late 1990s, KS was considered to cause total and definitive sterility. The first description in 1998 [11] reports 2 KS cases for which sperm could be extracted from testicular tissue and pregnancies have obtained after ICSI. Since this first result has been confirmed in several series in which testicular

**Table 1**

Studies were published since 2001 with more than 8 patients included (*n*: number patients in the report). The sperm retrieval rate (SRR) is variable from 20 to 69%.

Serie	<i>n</i>	SRR+
Westlander, 2001 [34]	19	21
Madgar, 2002 [14]	20	45
Vernaev, 2004 [15]	50	48
Schiff, 2005 [32]	29	69
Okada, 2005 [35]	51	51
Bakircioglu, 2006 [36]	74	56.7
Kyono, 2007 [37]	17	35.3
Koga, 2007 [38]	26	50
Ramasamy, 2009 [17]	68	66
Ferhi, 2009 [39]	27	29.6
Yarali, 2009 [40]	22	56
Selice, 2010 [41]	26	37.5
Bakircioglu, 2011 [42]	106	47
Greco, 2013 [43]	38	39.5
Madureira, 2014 [44]	65	38.5
Sabbaghian, 2014 [18]	134	28.4
Rohayem, 2015 young [19]	50	38
Rohayem, 2015 adult [19]	85	30.6
Majzoub, 2015 [33]	43	14
Vicdan, 2016 [45]	83	42.1
Chehrizi, 2017 [46]	134	28.4
Franik, 2018 [47]	9	33.3
Garolla, 2018 [30]	111	34.2
Ozer, 2018 [16]	110	20
Vloeberghs, 2018 [48]	138	34.8
Huang, 2020 [49]	66	34.6
Guo, 2020 [50]	184	43.5
Yucel, 2021 [51]	41	31
Renault, 2022 (submitted)	119	45.4
Total	1945	0.396

sperm extraction (TESE) allows fathering by assisted fertilization technologies [11]. Thereby, patients with KS may father their own children thanks to intracytoplasmic injection techniques using testicular sperm extracted from residual foci of preserved spermatogenesis [12,13].

## 4. Sperm retrieval rate and prognosis factors

Since 2001, several studies were published with more than 8 patients included in the report (Table 1). The sperm retrieval rate (SRR) is variable from 20 to 69% according to the authors. The cumulation of the series of the twenty last years is calculated in Table 1 and report a total of 1945 patients and an SRR average of 39.6%.

For 20 years, some studies reported different predictive factors among series published in Table 1. First, in only one multi-center study of 103 KS patients [14] testicular volume seems be bigger  $7.8 \text{ mL} \pm 2.5$  in case of SRR positive versus  $5.6 \text{ mL} \pm 1.2$  if SRR was negative. Among hormonal parameters, two studies reported that FSH level was significantly lower in case of SRR positive: 31.2 versus 40 UI [15] and 28.41 versus 33.08 [16]. In two other studies SRR were improved when Total testosterone level was

**Table 2**  
Impact of age on sperm recovery: studies review.

	Study (n)	TESE+ (n)		Age TESE+	TESE– (n)	Age TESE–	Significant
Okada, 2005 [35]	51	26	51	31 (25–40)	25	38 (28–43)	$P<0.0001$
Bakircioglu, 2006	74	42	56.7	$31.6\pm4.3$ (25–41)	32	$35.0\pm5.1$ (26–50)	$P=0.002$
Kyono, 2006 [37]	17	6	35.3	$30.2\pm3.9$	11	37.6 $\pm4.4$	$P<0.05$
Ramasamy, 2009 [17]	68	45	66	$32\pm5.3$	23	35 $\pm6.6$	$P=0.005$
Ferhi, 2009 [39]	27	8	29.6	$28.6\pm3.11$	19	33.9 $\pm4.5$	$P=0.002$
Yarali, 2009 [40]	22	22	56	$29.6\pm5.3$		35.1 $\pm6.6$	$P=0.008$
Bakircioglu, 2011 [42]	106	50	47	$32.5\pm4.9$	56	35.8 $\pm6.2$	$P=0.003$
Sabbaghian, 2014 [18]	134	38	28.4	$30.0\pm0.65$	96	33.68 $\pm0.6$	$P<0.016$
Chehrazai, 2017 [46]	134	38	28.4	$30.0\pm0.65$	96	33.68 $\pm0.6$	$P<0.05$
Ozer, 2018 [16]	110	22	20	$30.23\pm4.7$	88	33.3 $\pm5.4$	$P=0.012$
Vloeberghs, 2018 [48]	138	48	34.8	29.0 (26.5–3.0)	90	33.0 (30.0–37.0)	$P<0.001$

Study (n): number of patients in the study; TESE+ (n): number of TESE with success of sperm extraction; TESE– (n): number of TESE without sperm extraction.

**Table 3**  
Compared studies using exclusively conventional TESE (cTESE) and micro-TESE.

Reference cTESE	cTESE (n)	SRR + (n)	%	Reference mTESE	mTESE (n)	SRR + (n)	%
Vernaev, 2004 [15]	50	24	48	Schiff, 2005 [52]	29	29	69
Kyono, 2006 [37]	17	6	35.3	Bakircioglu, 2006	74	42	56.7
Ferhi, 2009 [39]	27	8	29.6	Koga, 2007 [38]	26	13	50
Madureira, 2014 [44]	65	25	38.5	Ramasamy, 2009 [17]	68	45	66
Majzoub, 2015 [33]	43	6	14	Yarali, 2009 [40]	22	22	56
Franik, 2018 [47]	9	3	33.3	Selice, 2010 [41]	26	9	37.5
Garolla, 2018 [30]	111	38	34.2	Bakircioglu, 2011 [42]	106	50	47
Renault, 2022	119	54	45.4	Sabbaghian, 2014 [53]	134	38	28.4
Fertipreserve (Submitted)				Rohayem, 2015 young [19]	50	19	38
				Rohayem, 2015 adult [19]	85	26	30.6
				Chehrazi, 2017 [46]	134	38	28.4
				Ozer, 2018 [54]	110	22	20
				Vloeberghs, 2018 [48]	138	48	34.8
				Huang, 2020 [49]	66	24	34.6
				Guo, 2020 [50]	184	80	43.5
Total	441	164	37.19	Total	1007	345	34.26

SRR + (n): the sperm retrieval rate/+: success.

higher at  $11.37 \pm 64.9$  nmol/ vs.  $7.28 \pm 4.05$  [17] and  $11.78 \pm 61.66$  versus  $8.07 \pm 0.79$  nmol/L [18]. According to Rohayem et al., 2015 [19], SRR is better in KS patients adolescent (54%) or adult (51%) when LH is lower than 17,5 associated to testosterone higher than 7.5 nmol/L.

Many studies have investigated the impact of age on sperm recovery and in Table 2, we reported the studies showing a significant difference of age between SRR positive and SRR negative. According to the selected 11 studies, an age greater than 35 seems to be associated with a decrease in the rate of sperm extraction. On the other hand, few studies reported fertility preservation in children and adolescent [20–25]. Among these studies, (Damani et al., 2001) report the first testicular sperm freezing for a young of 15 years. After this first experiment, other studies have been proposed for Klinefelter patients younger than 25. Van Saen et al., 2018 observed a poor sperm retrieval (5%) if they were less than 16 that confirmed the result of Rives et al., 2013. In 2015 previous preliminary result of Fertipreserve Study (23), observed positive sperm retrieval rate not significantly different from those of adults (SRR: 52%).

## 5. Conventional TESE/micro-TESE?

The techniques of medically assisted procreation have marked a step in the management of secretory azoospermia with the emergence of the technique of extraction of testicular spermatozoa (TESE) thus allowing their microinjection in oocyte or TESE-ICSI (TESE). The application of TESE-ICSI techniques was quickly proposed in KS offering the possibility of obtaining pregnancies in KS [27]. Since 1999, surgical techniques dedicated to sperm collection have marked a new advance with the development of micro-TESE. This technique consists of a testicular biopsy performed using a microscopic visual magnification (operating microscope) [28].

We selected studies including more than 8 patients and compared studies using exclusively conventional TESE (cTESE) and micro-TESE in Table 3. We did not observe significant different difference between these two technics.

Total positive sperm retrieval was at 37.2% using conventional and was not different compared to micro-TESE at 34.3%. Corona et al. in 2017 observed similar results by including different type of studies.

## 6. Androgen therapy

In the prospective study conducted in Lyon [29], previous testosterone treatment was withdrawn at least 9 months before TESE to avoid a possible decrease of gonadotropin secretion. Thirty-two patients, 14 in the Young group and 18 in the Adult group, had been under testosterone treatment. SRRs were 50% (16/32) for cases previously treated and 43.7% (38/87) for patients who had never received testosterone ( $P=0.539$ ). Duration of testosterone treatment was 25.5 [10–90] months in TESE+ and 34.0 [10–109] months in TESE– ( $P=0.546$ ). This lack of deleterious effect of a previous testosterone treatment was also found in 5 out of 6 other studies [19,22,23,30,31]. Schiff et al. [32] reported a deleterious effect, but they included only 5 patients with previous testosterone therapy. Treatments designed to increase testosterone secretion were often reported in retrospective studies, without consistent results for SRR in 7 out of 28 studies treating only patients with low testosterone levels [16,17,19,30,32,33], which introduces a selection bias that prevents comparison of SRR in treated versus non-treated patients. No treatment was administered before TESE in the Fertipreserve study. These data raise the question if it is necessary to expect the sperm cryopreservation before introducing androgen treatment.

## 7. Conclusion

For the last 20 years, several studies have shown that fertility in case of Klinefelter syndrome could be considerable in nearly 50% of cases. However, we observe variable result for success of sperm retrieval. The cohort of prospectively included KS patients is rare.

Personal data in prospective study (Fertipreserve study) of 159 KS confirmed this trend with a success of testicular sperm extraction in 45.4%.

Currently few predictive factors are able to predict success of sperm extraction. The increase of age seemed to be associated with less poor prognosis significantly after 35 years. On the other hand, a sample carried out before 16 years old does not improve positive sperm extraction rate. Androgen therapy does not seem to impact sperm retrieval. Further studies are necessary to determine the interest of new markers to predict the chance of sperm retrieval, taking into account age, hormonal therapy. The risk of spermatogenesis damage in the KS testis is important to appreciate as well as the psychological impact when trying to formulate fertility presentation to Klinefelter patients.

## Disclosure of interest

The authors declare that they have no competing interest.

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