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1 **Fertility preservation in young men with Klinefelter syndrome: a systematic review**

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22 sperm collection

23

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29

30 **ABSTRACT**

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32 **Background**

33 Klinefelter syndrome (KS) is the most common cause of genetic male infertility, as most
34 patients present azoospermia. In the testis, a massive decrease in the number of germinal cells
35 is observed and this can begin early in childhood. Thus, it is possible to collect spermatozoa
36 after sperm collection or thanks to testicular sperm extraction (TESE), but the chances finding
37 spermatozoa are decreasing with the age. Sperm collection or TESE should be performed as
38 early as possible. When KS is diagnosed during childhood or teens, fertility preservation could
39 be beneficial. The minimal age for proposing fertility preservation remains controversial and
40 there is no current recommendation about fertility preservation in young men with KS.

41

42 **Design**

43 In this context, we have conducted a systematic review of the results of fertility preservation in
44 young patients with KS to discuss the optimal age range for offering fertility preservation,
45 including or not a TESE.

46

47 **Results**

48 Six articles were included in the systematic review, with patients between 13 to 24 years-old.
49 Except for one, all young men agreed for sperm collection following masturbation.
50 Azoospermia was diagnosed in all patients presenting homogenous KS. One study reported the
51 presence of spermatozoa in the ejaculate of a young man with mosaic KS. Fifty-eight young
52 man for whom ejaculated sperm collection was unsuccessful have benefited from TESE.
53 Testicular spermatozoa were found and frozen in 27 patients out of the 58 (46.5%). The chances
54 of freezing viable testicular sperm between 14 and 23 years of age do not appear to depend on
55 age.

56

57 **Conclusion**

58 Fertility preservation should be proposed in young men, but the optimal age for proposing the
59 first sperm collection could be adapted according to the medical context and the psychological
60 maturity of the young man.

61

62

63 **Introduction**

64

65 Klinefelter syndrome (KS) is a clinical syndrome associated with a sex chromosome aneuploidy
66 characterized by the presence of cells with a 47,XXY karyotype, in male. Adult men usually
67 present with gynecomastia and tall stature associated to low testosterone and elevated
68 gonadotropin levels, as well as small and firm testes [1]. It is the most common cause of genetic
69 male infertility, as most patients present azoospermia. However, in some rare cases, when
70 aneuploidy is present in a mosaic state mixed with normal 46,XY cells, few spermatozoa can
71 be found in the ejaculate. Most often, KS is diagnosed during adulthood, when investigating
72 the cause of infertility. A testicular sperm extraction (TESE) is usually suggested in case of
73 azoospermia, and testicular spermatozoa can be retrieved in approximately 50% of TESE [2],
74 allowing *in vitro* fertilization (IVF) with intracytoplasmic sperm injection (ICSI). It has been
75 suggested that the prognosis of TESE is correlated with age and that the chances of retrieving
76 testicular spermatozoa are increased when TESE is performed as early as possible [3]. Indeed,
77 spermatogenesis alterations likely worsen with age: it starts *in utero*, evolves slowly during
78 childhood and accelerates during puberty. Histological study of a testicular tissue of an adult
79 with KS usually shows fibrosis and hyalinization of seminiferous tubes, associated with
80 hyperplasia of interstitial tissue [4]. In the testis, a massive decrease in the number of germinal
81 cells is observed and this can begin early in childhood. In patients with KS, the peri-pubertal
82 period is marked with progressive appearance of testicular fibrosis leading to progressive loss
83 of spermatogonial stem cells (spermatogonia) and decreased testosterone secretion by Leydig
84 cells leading to hypogonadism [5]. When KS is diagnosed during childhood or teens, fertility
85 preservation of ejaculated sperm or TESE could be beneficial. However, masturbation for
86 sperm recovery or testis surgery might be sensitive issues to be discussed with teenagers.
87 Furthermore, the minimal age for proposing fertility preservation remains controversial as only

88 few data are available in the literature, and there is no current recommendation about the
89 optimal age for proposing fertility preservation.

90 In this context, we have conducted a systematic review of the results of fertility preservation in
91 young patients with KS to discuss the optimal age range for offering fertility preservation,
92 including or not a TESE.

93

94 **Material and methods**

95

96 *Documentary research and eligibility criteria*

97 We searched for relevant reports published on PUBMED between January 2000 and April
98 2020, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
99 (PRISMA) recommendations (Stewart et al, 2015).

100 The search strategy consisted of using the following combined search terms: "((Teenager
101 [title/abstract]) or (Teenager [mesh terms]) or (prepubertal [title/abstract]) or (prepubertal
102 [mesh terms]) or (post pubertal [title/abstract]) or (post pubertal [mesh terms]) or (child*
103 [title/abstract]) or (child* [mesh terms]) or (young [title/abstract]) or (young [mesh terms]) or
104 (adolescent [title/abstract]) or (adolescent [mesh terms])) and ((Klinefelter [title/abstract]) or
105 (Klinefelter [mesh terms]) or (47,XXY [title/abstract]) or (47,XXY [mesh terms])) and
106 ((Fertility preservation [title/abstract]) or ((Fertility preservation [mesh terms]) or (sperm
107 freezing [title/abstract]) or (sperm freezing [mesh terms]) or (sperm banking [title/abstract]) or
108 (sperm banking [mesh terms]) or (sperm cryopreservation [title/abstract]) or (Testicular sperm
109 extraction [title/abstract]) or (Testicular sperm extraction [mesh terms]) or (Testicular sperm
110 retrieval [title/abstract]) or (Testicular sperm retrieval [mesh terms]) or (Sperm extraction
111 [title/abstract]) or (Sperm extraction [mesh terms]) or (Sperm retrieval [title/abstract]) or

112 (Sperm retrieval [mesh terms]) or (TESE [title/abstract]) or (TESE [mesh terms]) or
113 (microTESE [title/abstract]) or (microTESE [mesh terms]))".

114

115 *Selection of studies and data extraction*

116 After removal of duplicates, the articles were first pre-selected by reading the title and abstracts
117 by two independent readers (AL and CD). The pre-selected articles were then reclassified as
118 "excluded", "doubtful" or "included". The "doubtful" articles were discussed between AL and
119 CD to determine whether they can be retained or should be excluded. Any disagreement or
120 uncertainty was resolved by a third reviewer (NS). The articles preselected as "retained" were
121 then read in full text by two independent authors (AL and CD).

122

123 *Synthesis of data*

124 In order to characterize included studies, the following details were extracted: authors, year of
125 publication, country, type of study, sample size, chromosomal aberration (homogeneous or
126 mosaic), age group, sperm collection and results, TESE and results, testicular tissue histology.

127

128 **Results**

129

130 The database research allowed the selection of 80 articles, including five articles that were not
131 written in English or French. After reviewing 75 titles and abstracts, 10 full-text articles were
132 selected. Among them, six articles were included in the systematic review (Figure 1).

133

134 The number of patients in the included studies was small [4, 6-10], for a total number of 66
135 young men (Table 1). Included patients were 13 to 24 years-old. In one study, patients were
136 treated with at least 1 year of topical testosterone and aromatase inhibitor [8] and a study

137 specified that any testosterone treatment was withdrawn 6 months before the first semen
138 analysis and at least 9 months before testicular biopsy for patients [10]. Except for one, all
139 young men agreed for sperm collection following masturbation. Azoospermia was diagnosed
140 in all patients (n=63) presenting homogenous KS. One study reported the presence of
141 spermatozoa in the ejaculate of a young man with mosaic KS [7]. Fifty-eight young man for
142 whom ejaculated sperm collection was unsuccessful have benefited from TESE. Testicular
143 spermatozoa were found and frozen in 27 patients out of the 58 (46.5%). Two teams reported
144 freezing of testicular tissue or germ cells in patients with negative TESE [6, 9]. The chances of
145 finding spermatozoa after TESE do not seem to depend on male age before 24 years-old (**Figure**
146 **2**). Regarding the procedure, microTESE is being increasingly used, especially among recent
147 studies, and bilateral biopsy is usually preferred.

148

149 **Discussion**

150

151 Massive apoptosis of spermatogonia in young men with KS has led health care professionals to
152 offer fertility preservation at young ages, as early as prepubescent stage in some cases [11].
153 Nevertheless, in the light of current evidence, the benefits of fertility preservation before
154 puberty are highly questionable [12], since the chances of finding mature spermatozoa are null.
155 A survey was recently submitted to various health professionals who are involved in the
156 healthcare for KS patients (endocrinologists, pediatricians, urologists). This revealed that all
157 practitioners promote fertility preservation during "late" puberty [13]. Similarly, in a recent
158 review, Franik et al. underlined the low chances of obtaining mature spermatozoa for young
159 patients under 16 years old as opposed to patients in the range of 16 to 30 years old [14]. Hence,
160 the authors do not recommend fertility preservation before the age of 16. Although the number
161 of patients who met the inclusion criteria of the present systematic review is limited, the results

162 show that the chances of finding spermatozoa in testicular tissue seem to be independent of age
163 between 14 and 23 years old and do not seem to decrease with age between 14 and 18 years old
164 in young men with KS. Consequently, we propose that fertility preservation could be offered
165 to young patients from the age of 18.

166

167 While it remains difficult to determine an optimal age for offering fertility preservation in
168 young men with KS [14], several parameters should however be considered. The initiation of
169 androgen substitution therapy as early as possible following the diagnosis, including at puberty,
170 has been advocated since a long while [15] in order to prevent the clinical consequences of
171 hypogonadism. However, androgen therapy has a well-known detrimental effect on
172 spermatogenesis [16]. Since hypergonadotropic hypogonadism may be compensated in 60% of
173 KS adolescents between 15 and 23 years old resulting in a minimal endocrine testicular function
174 that is sufficient to obtain a normal pubertal development [17], it may be preferable to defer
175 fertility preservation to the age of 18 years old and start androgen therapy afterwards. If fertility
176 preservation cannot be offered before the initiation of androgen treatments, optimization of
177 intra-testicular testosterone levels by adjunction of anti-aromatases, anti-estrogens or hCG may
178 be considered [8, 18]. As these treatments do not seem to compromise the chances of finding
179 sperm in testicular tissue, they could constitute interesting alternatives to androgen disruption
180 window, even if a potential impact of hormonal treatments on the quality of the spermatozoa,
181 such as epigenetic marks, is not known [19]

182 Independently from age, the karyotype is predictive of the chances of retrieving spermatozoa.
183 In non-mosaic situations, all the young KS men included in this study displayed azoospermia.
184 Although spermatozoa may be found in the ejaculate of some individuals [17], this remains a
185 rare situation that likely depends on the tissue-mosaicism, in particular in the testes. Hence,
186 young men should be prepared to the risk of a negative outcome and the possible need of TESE.

187 Other clinical (testicular volume) or biological (hormonal status) markers were not sufficiently
188 well documented in the selected studies to be used as prognostic markers in this review.

189 Importantly, a psychological support to the patients is recommended when proposing fertility
190 preservation. Even if young men diagnosed with KS early in childhood are usually informed at
191 a very early stage and may be comfortable with these questions, it is important to anticipate
192 fertility issues beforehand. The possible absence of spermatozoa following semen collection
193 and after TESE should be discussed with the young patient and his parents if he is minor. Sperm
194 donation and adoption are also topics that can be addressed, even if some adolescents may not
195 be mature enough or psychologically prepared to deal with these issues and anticipate the
196 difficulties of an infertility journey [20]. Although it is usually admitted that maturity is
197 acquired with age, each young man is different and evolves at his own pace. Consequently, the
198 age of fertility preservation proposal can therefore be adapted to the emotional development of
199 the young adult.

200 The surgical techniques of testicular biopsy were reported in the articles included in this review
201 but available data is not sufficient to compare the efficiency of the different procedures.
202 However, in young patient with testicular hypotrophy, microTESE may be more efficient and
203 less invasive although at higher risk of postoperative hematoma [21].

204

205 **Conclusion**

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207 Data published in young KS men raise the question of the minimal age to start fertility
208 preservation procedures. The conventional approach is to look for spermatozoa in semen first,
209 and, in case of azoospermia, suggest surgical extraction. The chances to obtain enough viable
210 mature spermatozoa to be cryopreserved in the testicular biopsy seem to be independent of age
211 between 14 and 23 years old. Although this result remains to be further confirmed in larger

212 series, it suggests that there would be no loss of chance to defer fertility preservation after TESE
213 to the age of 18 years old for azoospermic KS young men. The optimal age for proposing the
214 first sperm collection could hence be adapted according to the psychological maturity of the
215 young man.

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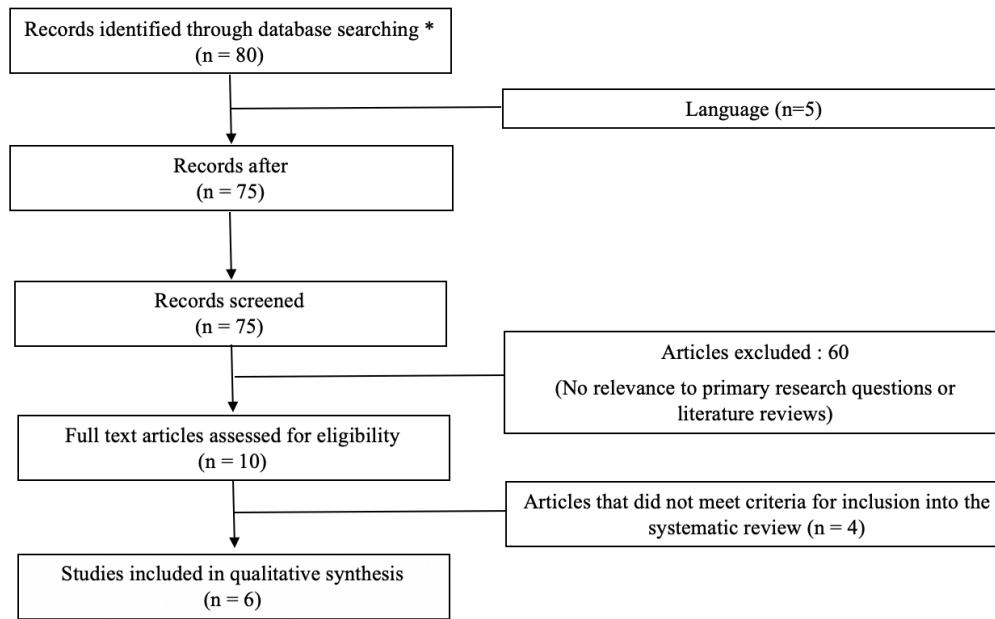


Figure 1 : Flow chart of study selection for systematic review

* PUBMED : between january 2000 and March 2020

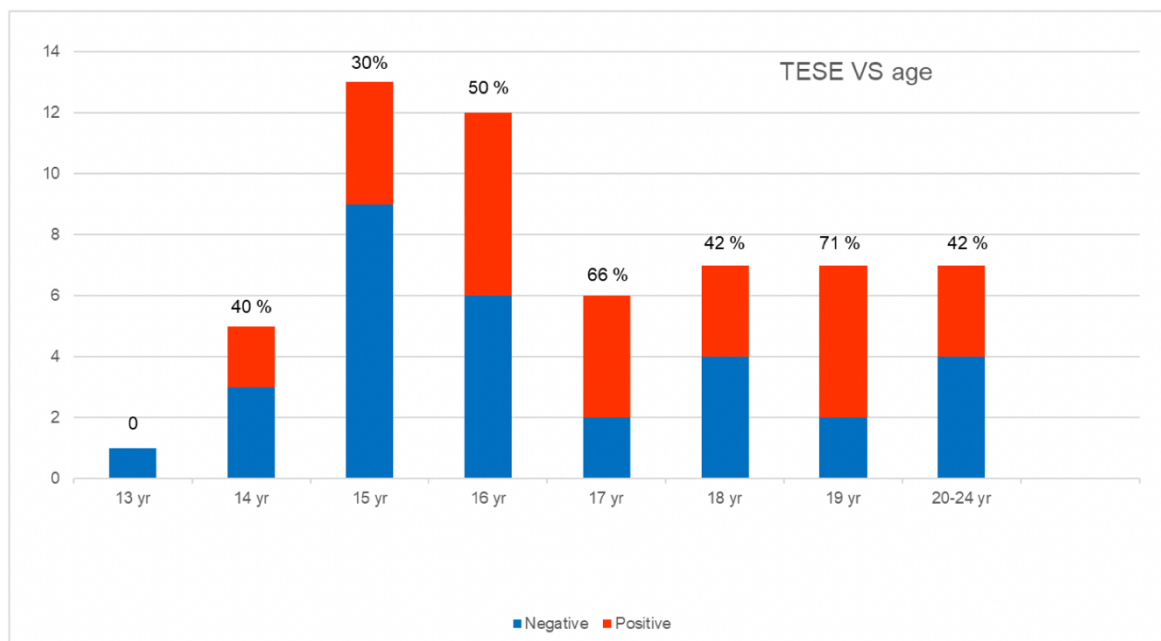


Figure 2 : TESE results according to patient's age

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Authors, year, journal, country	Study	Enrollment (n=)	Age	Genotype	Sperm collection (SC)	SC Results	Testicular sperm extraction (TESE)	TESE Results	Cryopreservation	Testicular tissue histology	
										Spermatogenesis	Fibrosis
Damani MN <i>et al.</i> , 2001, Fertil Steril, USA	Case Report	1	15 years old	Non mosaic	n = 1	(+) = 0 (-) = 1	n=1 micro TESE unilateral	(+) = 1 (-) = 0	SPZ = 0 TESE = 1 TT = 0	-	NA
Van Saen D <i>et al.</i> , 2012, Hum Reprod, Belgium	Retrospective study	7	13-16 years old	Non mosaic	n = 7	(+) = 0 (-) = 7	n=7 TESE unilateral	(+) = 0 (-) = 7	SPZ = 0 TESE = 0 TT = 7	Incomplet (n=5)	No
Rives N <i>et al.</i> , 2013, Hum Reprod, France	Retrospective study	8	15-17 years old	Non mosaic (n=7) Mosaic (n=1)	n = 8	(+) = 1 (-) = 7	n=5 TESE bilateral	(+) = 1 (-) = 4	SPZ = 1 TESE = 1 TT = 0	incomplet (n=1)	Yes
Mehta A <i>et al.</i> , 2013, Fertility and Sterility, USA	Case series	10 (*)	14-22 years old	Non mosaic	n = 10	(+) = 0 (-) = 10	n = 10 micro TESE 4 unilateral 6 bilateral	(+) = 7 (-) = 3	SPZ = 0 TESE = 7 TT = 0	NA	NA
Nahata L <i>et al.</i> , 2016, The Journal of Pediatrics, USA	Clinical trial	15	15-24 years old	Non mosaic	n=14	(+) = 0 (-) = 14	n=10 micro TESE unilatérale	(+) = 5 (-) = 5	SPZ = 0 TESE = 4 TT = 10	NA	NA
Plotton I <i>et al.</i> , 2016, The Journal of Pediatrics, France	Clinical trial	25 (**)	15-22 years old	Non mosaic	n = 25	(+) = 0 (-) = 25	n=25 TESE bilateral	(+) = 13 (-) = 12	SPZ = 0 TESE = 13 TT = 0	NA	NA

Table 1 : Characteristics of studies reporting fertility preservation in young men with Klinefelter syndrome

(*) Patients with Klinefelter syndrome treated with at least 1 year of topical testosterone and aromatase inhibitor.

(**) Testosterone treatment was withdrawn 6 months before the first semen analysis and at least 9 months before testicular biopsy.

(+) : positive, (-) : negative, NA : Not available : spermatogonia, SPZ : spermatozoa from semen, TESE : spermatozoa from biopsy testicular, TT : testicular tissue