Should non-mosaic Klinefelter syndrome men be labelled as infertile in 2009?

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BACKGROUND: Klinefelter syndrome is a common genetic condition. Affected non-mosaic men are azoospermic and have been labelled as infertile. Despite reports that these men can have children using assisted reproduction techniques, it is not common practice in the UK to offer sperm retrieval to these men.

METHODS: Medline and EMBASE (1980–2009) were searched independently by two authors and all studies involving surgical sperm retrieval in non-mosaic Klinefelter syndrome were included. The primary outcome was success of surgical sperm retrieval and the secondary outcome was live birth rate.

RESULTS: The overall success rate for sperm retrieval was 44%, with a higher rate of success using micro-dissection testicular sperm aspiration (micro-TESE) (55%). This, along with ICSI, has led to the birth of 101 children. However, there are no known predictors for successful sperm retrieval. Although there are concerns about genetic risk to the offspring of non-mosaic Klinefelter patients, this risk has not been found to be greater than that of patients with non-obstructive azoospermia with normal karyotype.

CONCLUSIONS: It is possible for a man with non-mosaic Klinefelter to father a child. However, before these techniques are offered, some ethical issues need to be explored.

Key words: Klinefelter syndrome / infertility / micro TESE / TESE / testicular sperm extraction

Background
Klinefelter syndrome, first described in 1942, is a common genetic condition affecting approximately 1 in 500–1000 newborn males (Klinefelter et al., 1942; Foresta et al., 1999). Various genotypes are associated with this condition, the most common being 47XXY in up to 80% of non-mosaic Klinefelter syndrome patients. Other less common variants are 48XXXY, 49XXXXY and 48XXYY (Foresta et al., 1998). The extra chromosome is inherited either from the mother or father at an approximately equal ratio (Thomas and Hassold, 2003). Although, the phenotypic appearance of a male with Klinefelter syndrome varies widely, common appearances are of enlarged breasts, sparse facial and body hair as well as small, firm, testes. Other features often seen are increased height and decreased muscle mass.

It is estimated that only 25% of men with Klinefelter syndrome are actually diagnosed (Bojesen et al., 2003); and many will present later in life with infertility. Men with Klinefelter syndrome are thought to make up 3% of infertile men and 11% of men with azoospermia (Foresta et al., 1999). Infertility is caused by degeneration of the germ cells in Klinefelter males but the exact mechanism by which this occurs is not fully understood.

Natural history of testicular development in Klinefelter syndrome
From birth to 5 months of age, the testicular volume rises to a maximum of 0.44 cm³. After this, the volume declines again and reaches its minimum around 9 months, to remain approximately the same size till the age of six (Kuijper et al., 2008). The observed significant rise in testicular volume coincides with the so called ‘mini-puberty’ which describes a peak in gonadotropic hormones around 3–4 months of age (Andersson et al., 1998; Grumbach, 2005). Testosterone and LH return to a minimum at 6–9 months. Hormonal
stimulation by activation of the hypothalamic–pituitary–testicular axis remains quiescent until puberty. Puberty is driven by increasing levels of GnRH from the hypothalamus that causes a rise in the levels of FSH, LH and testosterone. Physical changes occur with development of body and pubic hair, deepening of the voice and enlargement of the testes which continues until it reaches adult size.

Prepubertal boys with Klinefelter syndrome have been shown to have normal testosterone, FSH, LH and inhibit B levels (Christiansen et al., 2003; Salbenblatt et al., 1985; Topper et al., 1982; Wikstrom et al., 2004, 2006a, b). At puberty, there is an initial increase in testicular size to ~6 ml in Klinefelter boys. However, as testosterone levels increase, there is acceleration of germ cell depletion, hyalinization of tubules, Sertoli cell degeneration and hyperplasia of the Leydig cells (Lahlou et al., 2004; Ross et al., 2005; Askglaede et al., 2006). This results in a decrease in testicular volume to prepubertal size (Ratcliffe et al., 1986; Robinson et al., 1986). The degeneration process is accompanied by a relative Leydig-cell insufficiency reflected by impaired serum testosterone levels and increasing LH levels. The initial adolescent rise in testosterone is relatively normal but from around the age of 14 years, testosterone levels seem to level off into the low-normal range (Topper et al., 1982; Salbenblatt et al., 1985; Wikstrom et al., 2004). However, such testosterone levels seem sufficient to allow normal onset and progression of puberty and development of satisfactory secondary sexual characteristics in Klinefelter syndrome boys (Wikstrom and Dunkel, 2008). There are suggestions that in Klinefelter Syndrome, germ cell differentiation is at least partially arrested at the spermatogonium or early primary spermatocyte stage. It seems that in Klinefelter syndrome, spermatagonia have difficulty entering meiosis; instead they proceed to apoptosis at the onset of puberty (Wikstrom and Dunkel, 2008).

Testicular histology in adult with Klinefelter syndrome is characterized by extensive fibrosis and hyalinization of seminiferous tubules and hyperplasia of interstitium (Klinefelter et al., 1942). In addition there is hypergonadotrophic hypogonadism (low-normal testosterone, high FSH and LH levels and undetectable inhibit B) (Salbenblatt et al., 1985; Anawalt et al., 1996; Foresta et al., 1999; Christiansen et al., 2003, Lahlou et al., 2004; LanFranco et al., 2004; Wikstrom et al., 2004).

The extra X chromosome in Klinefelter syndrome is thought to be responsible for infertility by causing degeneration of the germ cells (Askglaede et al., 2006). Some reports suggest that the degeneration of germ cells start early in infancy, leading to the absence or a significantly reduced number of germ cells even before puberty (Mikamo et al., 1968; Murken et al., 1974; Ratcliffe, 1982; Coerdt et al., 1985; Muller et al., 1995). The reduced number of germ cells has been seen in testicular biopsies on fetuses aborted at mid-trimester (Murken et al., 1974; Autio-Harainen et al., 1980; Coerdt et al., 1985). However, two authors have reported normal testicular histology in 47XXY fetuses aborted at 17 and 20 weeks (Gustavson et al., 1978; Flannery et al., 1984). There may already be some impairment of Leydig cell function at birth (Wikstrom and Dunkel, 2008), however, there are controversies regarding the presence of hypoandrogenism in infancy.

Options for fertility

About 10% of patients with Klinefelter syndrome have a mosaic form (46XY/47XXY) in which the presence of sperm in the ejaculate and subsequent paternities have been reported (Emre Bakircioglu et al., 2006). Men with non-mosaic Klinefelter syndrome have azoospermia, and are thus traditionally labelled as infertile. Their options for children usually rest with donor insemination or adoption. In 1982, a case report was published demonstrating spontaneous conception of a child from a non-mosaic Klinefelter father (Laron et al., 1982). Since then more cases have been reported and sperm have been found in 7.7 and 8.4% of ejaculated semen samples of non-mosaic Klinefelter patients (Kitamura et al., 2000; LanFranco et al., 2004). These observations led to a stepwise demonstration of spermatogenic foci in many of these patients (Heller and Nelson, 1945; Ferguson-Smith, 1959; Steinberger et al., 1965; Skakkebaek, 1969; Skakkebaek et al., 1969; Frooland and Skakkebaek, 1971; Foresta et al., 1999; Sciurano et al., 2009). With the ability to retrieve testicular sperm through testicular sperm extraction (TESE) and the expansion of assisted reproduction, this group of men have been able to consider the possibility of having their own genetic child.

The first such child was born in 1997 using Intracytoplasmic Sperm Injection (ICSI) for a non-mosaic Klinefelter man (Bourne et al., 1997). Since then many more births have been reported (Denschlag et al., 2004). Foresta et al. (1999) performed FISH on testicular tissue of ten non-mosaic Klinefelter men and found residual spermatogenesis in two patients and Sertoli cells were identified cytologically in all 10. Despite the published evidence, it is not common practice to offer surgical sperm retrieval to these men, at least in the UK. Hence we decided to explore the success of surgical sperm retrieval in men with non-mosaic Klinefelter syndrome by way of a systematic review. In addition, we have also attempted to explore the outcome of pregnancies in these couples.

Materials and Methods

Medline (1982–2009) and EMBASE (1982–2009) were searched using the keywords ‘Klinefelter’ ‘infertility’; ‘assisted conception’ or ‘IVF’ or ‘sperm injection’ by two authors (A.M. & G.F.) independently. Any discrepancies for inclusion of the studies were resolved after discussions. Contact with authors of primary studies was attempted wherever appropriate. Guidelines for systematic reviews of observational studies (MOOSE guidelines) were followed (Group et al., 2000). All cross references were hand searched as were relevant conference abstracts. All types of studies (randomized controlled trials and observational studies) were selected. There were no language restrictions.

Inclusion criteria

We included all articles that described surgical sperm retrieval in non-mosaic Klinefelter syndrome patients. Details of the method of sperm retrieval, the number of patients, number of attempts and the success rate were extracted. We included studies that involved mosaic Klinefelter syndrome men only if we were able to extract the data exclusive to non-mosaic patients. Case series were included but case reports were excluded to avoid bias when evaluating the success of sperm retrieval. To explore pregnancy outcomes, we included both case series and reports where assisted reproduction techniques have been used irrespective of the method of sperm collection (from ejaculate or surgical sperm retrieval).

Exclusion criteria

We excluded studies that did not specify the genotype of the men to avoid any bias in the results as it is well known that mosaic Klinefelter syndrome
men can father spontaneous pregnancy. In this review, we have concentrated on non-mosaic Klinefelter syndrome men only.

Outcome measures
The primary outcome was success rate of surgical sperm retrieval and the secondary outcome measure was live birth rate.

Results
We were able to include 13 articles involving 373 men with non-mosaic Klinefelter syndrome. Schiff et al. (2005) was excluded as they included three patients with mosaic Klinefelter syndrome which we were unable to identify separately. The success rate of surgical sperm retrieval was 72% in this study.

The overall success rate of extracting sperm from patients with Klinefelter syndrome is 44% (range 16–60%). The two methods of retrieving sperm have been described by these studies: TESE and micro-dissection TESE. When stratifying the results based on these two techniques, a higher success rate with micro-TESE [42% (95/228) versus 55% (61/110)] was found (P = 0.010) (http://www.graphpad.com/quickcalcs/contingency2.cfm). Characteristics of the studies have been summarized in Table I.

Table II summarizes the data on children born to Klinefelter fathers. To date there have been 101 genetic children born to non-mosaic Klinefelter syndrome patients after assisted reproduction techniques and two children born after spontaneous conception published in the literature. There have been 12 twin and 3 triplet conceptions. Most of these cases did not have Preimplantation Genetic Diagnosis. Some studies (Staessen et al., 1996; Reubinoff et al., 1998; Tourmaya et al., 1998) reported using PGD for these patients, but interestingly, when PGD has been offered to couples, many have declined (Palermo et al., 1998; Ron-El et al., 2000a, b; Bergere et al., 2002; Poulakis et al., 2001). In other centres where PGD is not offered, prenatal diagnosis was performed and was accepted by couples (Kitamura et al., 2000; Rosenlund et al., 2002; Komori et al., 2004; Yarali and Bozdag, 2006; Koga et al., 2007). Two fetuses were diagnosed prenatally as 47XXX genotype. Both were part of triplet pregnancies which were subsequently reduced to twin pregnancies (Ron-El et al., 2000a, b; Frieler et al., 2001). Post-natal genotyping of the offspring of Klinefelter syndrome men has been carried out and there have been no published cases of Klinefelter syndrome in the children born to these men.

Discussion
The knowledge that men with non-mosaic Klinefelter syndrome have a potential for fertility has been aided by developments in assisted reproduction techniques. The presence of sperm in the ejaculate was an important finding but not all the spermatozoa found are capable of fertilization (Frieler et al., 2001). By carrying out surgical sperm retrieval, men with Klinefelter syndrome, even without having any sperm in ejaculate, can have ICSI. We have shown that with current techniques and skill levels, the success of surgical sperm retrieval in non-mosaic Klinefelter syndrome men is approximately 44% (16–60%). The rate is even higher with micro-dissection TESE (55%), which is similar to the success rate of surgical sperm retrieval in patients with non-obstructive azoospermia with normal karyotype.

This review has highlighted the potential for these men to father children. In non-mosaic Klinefelter syndrome, the first pregnancy using surgical sperm retrieval was published in 1996 (Staessen et al., 1996) and the first child born using ICSI was in 1997 (Bourne et al., 1997). There have now been 101 children born to fathers with non-mosaic Klinefelter syndrome and this may be an underestimation of the total numbers, as some may not be published. Why, therefore, is this option not offered routinely to affected men in the fertility clinic or why is it not discussed with men who are diagnosed with this condition in childhood? This may be because there are unanswered questions in this area, such as the genetic risks to the offspring, the ability to predict success of sperm retrieval and the appropriate time for such a discussion.

What are the genetic risks to offspring?
Although it is possible to obtain sperm using surgical sperm retrieval and achieve fertilization using ICSI, there are concerns that offspring will be at risk of inheriting genetic problems. There is evidence of increased numerical abnormalities in spermatozoa from an XXY male. Rives et al. (2000) showed 97.9% normal haploid spermatozoa (n = 10 123) in a non-mosaic patient giving an aneuploidy rate of around 2%. Similar results were obtained by Levron et al. (2000). Various theories have been postulated to explain the rate of aneuploidy: (i) The XXY testis might be populated by XXY germ cells, resulting in formation of both normal and disomic spermatozoa or (ii) the tests might be populated by XY germ cells but owing to deficiencies in the XXY testicular environment, these germ cells might be susceptible to various meiotic errors.

It is believed that 47XXXY germ lines are unable to undergo mitosis and meiosis, probably because of the presence of two functional X chromosomes. Therefore any sperm found in such patients probably originates from normal germ lines. Despite these considerations, other authors have proposed that 47XXXY germ cells are in fact, able to undergo meiosis and there is abnormal meiotic segregation leading to abnormal gametes which if fertilized lead to abnormal offspring (Guttenbach et al., 1997; Estop et al., 1998; Foresta et al., 1999; Hennebicq et al., 2001; Levron et al., 2000; Yamamoto et al., 2002). Mouse studies on XXY male mice have shown that the few germ lines that are found in adult tests are exclusively of XY karyotype. Therefore meiotic aneuploidies that are found in the sperm of these mice most probably relate to a compromised testicular environment rather than to abnormal spermatogonial cell lines (Mroz et al., 1999). Others believe that non-mosaic Klinefelter patients who produce sperm are thought to be germ cell mosaics and it is the 46XY cells only that can complete meiosis (Rives et al., 2000; Blanco et al., 2001; Bergere et al., 2002; Siffroi et al., 2003). It is further thought that the abnormal testicular environment affects the spermatocytes and increases segregation errors. A recent study (Sciurano et al., 2009) demonstrated spermatogonial foci in 55% of non-mosaic Klinefelter patients (6/11). Subsequent analysis with FISH showed all 92 spermatoagonia to be euploid 46XY and can therefore form normal gametes. This provides a rationale for the high success rate in TESE combined with ICSI in this group of men.
<table>
<thead>
<tr>
<th>Author</th>
<th>No. of pts</th>
<th>Genotype</th>
<th>Mean/median age success failure</th>
<th>Drug therapy</th>
<th>No. of attempts</th>
<th>Procedure</th>
<th>Successful sperm retrieval (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tourmaye (1997)</td>
<td>15</td>
<td>Non-mosaic</td>
<td>Not available</td>
<td>nil</td>
<td>17</td>
<td>TESE</td>
<td>8/15 (47)</td>
<td></td>
</tr>
<tr>
<td>Friedler et al. (2001)</td>
<td>12</td>
<td>Non-mosaic</td>
<td>28 ± 3.2; 27.9 ± 4.5</td>
<td>nil</td>
<td>10</td>
<td>TESE</td>
<td>5/12 (42)</td>
<td>2 patients has sperm in ejaculate but subsequently underwent SSR (1x immotile sperm, 1x failed ICSI)</td>
</tr>
<tr>
<td>Levron et al. (2000)</td>
<td>20</td>
<td>Non-mosaic</td>
<td>Not available</td>
<td>nil</td>
<td>20</td>
<td>TESE</td>
<td>8/20 (40)</td>
<td>Successful TTB was noted in men with 47XXY and 46XY spermatogonia in seminiferous tubules</td>
</tr>
<tr>
<td>Yamamoto et al. (2002)</td>
<td>24</td>
<td>Non-mosaic</td>
<td>Not available</td>
<td>nil</td>
<td>20</td>
<td>TTB</td>
<td>12/24 (50)</td>
<td>Unsuccessful TTB showed only 47XXY spermatogonia</td>
</tr>
<tr>
<td>Madgar et al. (2002)</td>
<td>20</td>
<td>Non-mosaic</td>
<td>32.5 32</td>
<td>nil</td>
<td>20</td>
<td>TESE</td>
<td>9/20 (45)</td>
<td>No significant difference in FSH, LH</td>
</tr>
<tr>
<td>Westlander et al. (2003)</td>
<td>18</td>
<td>Non-mosaic</td>
<td>30.8 ± 2.2; 34.5 ± 5.3</td>
<td>nil</td>
<td>18 Repeat procedure done in the 5 successful patients in a second ICSI cycle</td>
<td>TESE</td>
<td>5/18 (28)</td>
<td>No significant difference in FSH, LH</td>
</tr>
<tr>
<td>Seo et al. (2004)</td>
<td>36</td>
<td>25 non-mosaic</td>
<td>31.2 ± 1.9; 32.3 ± 3.4</td>
<td>nil</td>
<td>36</td>
<td>TESE</td>
<td>4/25 non-mosaic (16)</td>
<td>No significant difference in success for age, FSH, testosterone, testicular volume</td>
</tr>
<tr>
<td>Vernaève et al. (2004)</td>
<td>50</td>
<td>Non-mosaic</td>
<td>29.5 ± 1.3; 32.8 ± 1.6</td>
<td>nil</td>
<td>24</td>
<td>TESE</td>
<td>24/50 (48)</td>
<td>No predictive power to age, testicular volume, FSH, FSH:LH ratio, testosterone, ASI</td>
</tr>
<tr>
<td>Okada et al. (2005a, b)</td>
<td>10</td>
<td>Non-mosaic</td>
<td>Not available</td>
<td>nil</td>
<td>10</td>
<td>mTESE</td>
<td>6/10 (60)</td>
<td>No significance in success between non-mosaic and mosaic Klinefelter syndrome</td>
</tr>
<tr>
<td>Okada et al. (2005a, b)</td>
<td>51</td>
<td>Non-mosaic</td>
<td>31 (25–40); 38 (28–43)*</td>
<td>nil</td>
<td>51</td>
<td>TESE</td>
<td>26/51 (51)</td>
<td>No significance in success between FSH, LH, testosterone and testicular volume</td>
</tr>
<tr>
<td>Emre Bakircioğlu et al.</td>
<td>74</td>
<td>Non-mosaic</td>
<td>31.6 ± 4.3; 35 ± 5.1</td>
<td>nil</td>
<td>74</td>
<td>mTESE</td>
<td>42/74 (57)</td>
<td></td>
</tr>
<tr>
<td>Kyono et al. (2007)</td>
<td>17</td>
<td>Non-mosaic</td>
<td>30.2 ± 3.9; 37.6 ± 4.4</td>
<td>nil</td>
<td>17</td>
<td>TESE</td>
<td>6/17 (35)</td>
<td>Success was significantly improved in lower age group; no significant difference in LH, FSH, testosterone and testicular volume</td>
</tr>
</tbody>
</table>

Continued
Moreover, it is suggested that although the rates of aneuploidy are slightly higher, they are much lower than in XYY males. In fact, the risk of abnormality is about the same as for azoospermic men with normal karyotype (Levron et al., 2000; Palermo et al., 2002). This leads to further debate about whether there is any need for Klinefelter syndrome patients to be offered preimplantation genetic diagnosis. Patients considering PGD should be advised of the current aneuploidy rates in Klinefelter syndrome and be advised of the potential risk to the embryo of PGD (Hardy et al., 1990). This should be balanced against the risk of chorionic villus sampling or amniocentesis in the event of an ongoing pregnancy. There is an increased cost and a delay in embryo transfer until blastocyst stage for those undergoing PGD. A small study of 20 Klinefelter syndrome patients found 54% of the embryos to be normal on preimplantation genetic diagnosis (Staessen et al., 2003). Of the 46% that were abnormal, there was a significant increase in sex chromosome abnormalities (3.1 versus 13.2%; control versus Klinefelter syndrome), autosomal abnormalities (5.2 versus 15.6%), ploidy abnormalities (4.3 versus 10.6%) and abnormalities in chromosomes 18 and 21. A higher frequency of disomy 21 has also been observed in spermatozoa from Klinefelter syndrome men (Hennebicq et al., 2001). It has also been shown that there is an increase in chromosomal abnormalities in sperm retrieved surgically from non-obstructive azoospermic men (even when they have normal karyotype) compared with that from obstructive azoospermia and to ejaculated sperm (11.4 versus 1.8 versus 1.5%, respectively) especially for chromosomes XY, 18 and 21 (Palermo et al., 2002).

To date, there have been two published reports of triplet pregnancies undergoing selective reduction following detection of a Klinefelter syndrome genotype (Ron-El et al., 2000a, b; Freidler et al., 2001) and there have been reports of additional X chromosomes being detected in embryos undergoing PGD prior to transfer (Reubinoff et al., 1998).

Can we predict the success of sperm retrieval?

Various factors that have been explored to predict the success rate of surgical sperm retrieval include physical features, biochemistry (serum testosterone, FSH, LH), testicular volume, FISH of lymphocytes and testicular ultrasound. The current studies involve small number of patients and the results obtained have not provided consistent answers. One study with 20 patients found a significantly larger testicular volume and serum testosterone level to be a marker (Madgar et al., 2002) but this has been disputed by other studies involving similar numbers of non-mosaic Klinefelter syndrome men (Tsujimura et al., 2007; Seo et al., 2004; Vernaeve et al., 2004; Koga et al., 2007). The most promising predictive factor has been the age of the man at biopsy (Okada et al., 2005a, b; Kyono et al., 2007). In 50% of cases, there was successful retrieval of spermatozoa in a group of men with a mean age of 36 years (13 from 26 patients, Koga et al., 2007). The mean/median age of men with successful and unsuccessful sperm retrieval is given in Table I and generally shows younger ages in the successful groups. Unfortunately, however, individual patient data was available in only two studies. Hence we cannot aggregate the data to reach a definite conclusion.
### Table II  Summary of published pregnancies of Klinefelter syndrome patients

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients with ejaculated sperm</th>
<th>No. of patients with TESE sperm</th>
<th>Pregnancies</th>
<th>Miscarriages (biochemical pregnancy)</th>
<th>Live births</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laron et al. (1982)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Spontaneous conception</td>
</tr>
<tr>
<td>Terzoli et al. (1992)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Spontaneous conception</td>
</tr>
<tr>
<td>Honda et al. (2000)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 embryos transferred</td>
</tr>
<tr>
<td>Staessen et al. (1996)</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1 biochemical pregnancy</td>
<td>0</td>
<td>Preimplantation genetic diagnosis performed on all embryos</td>
</tr>
<tr>
<td>Bourne et al. (1997)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>Frozen sperm, unsuccessful transfer at first cycle. Two embryos transferred at second cycle—twin birth</td>
</tr>
<tr>
<td>Hinney et al. (1997)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Miscarriage at 9 weeks gestation, normal karyotype</td>
</tr>
<tr>
<td>Touraye et al. (1997)</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>1 biochemical pregnancy</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Palemo et al. (1997)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>Sperm retrieved by testicular fine needle aspiration; PGD of one embryo showed 47XXY</td>
</tr>
<tr>
<td>Reubinoff et al. (1998)</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Pregnancy initially with 3 sacs (early fetal demise); twin birth</td>
</tr>
<tr>
<td>Nodar et al. (1999)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ron-El et al. (1999)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Kitamura et al. (2000)</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Levron et al. (2002)</td>
<td>0</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Ron-El et al. (2000a, b)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>One triplet and one twin pregnancy</td>
</tr>
<tr>
<td>Ron-El et al. (2000a, b)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>One live birth using fresh sperm; three cycles using frozen testicular sperm—miscarriage, failed implantation and successful twin pregnancy</td>
</tr>
<tr>
<td>Greco et al. (2001)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>Twin birth</td>
</tr>
<tr>
<td>Kyono et al. (2001)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Poulakis et al. (2001)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cruger et al. (2001)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Friedler et al. (2001)</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>66% fertilization rate at ICSI—fresh sperm 3 embryos transferred per patient. Triplet pregnancy reduced to twin after one with 47XXY diagnosed prenatally</td>
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<td>(2 cycles described)</td>
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<td>58% fertilization rate at ICSI—cryopreserved thawed testicular sperm—1 healthy twin pregnancy</td>
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<td>Rosenlund et al. (2002)</td>
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<td>First attempt did not fertilize with fresh testicular sperm. Two attempts with frozen sperm—2 embryos transferred, no pregnancy; 2 embryos transferred, 1 pregnancy</td>
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<td>Tachdjian et al. (2003)</td>
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<td>2 embryos transferred/cycle. 2 ICSI cycles/couple—1 fresh, 1 cryopreserved embryos</td>
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<th>Author</th>
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<th>No. of patients with TESE sperm</th>
<th>Pregnancies</th>
<th>Miscarriages (biochemical pregnancy)</th>
<th>Live births</th>
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TESE, Testicular Sperm Extraction.
seems this label is out of date and patients should be counselled in light of these new advances, even if the diagnosis is made in adulthood.

**Conclusion**

There seems to be little doubt that there is a chance for men with Klinefelter syndrome to father a genetic child. Obviously the success is not 100% but the label of infertile should be re-evaluated in the light of recent developments. There is little or no spontaneous fertility but significant chances through the use of assisted conception techniques. Males diagnosed with Klinefelter syndrome need to be informed about and offered such choices. However, before their hopes are raised, there are ethical issues which need to be clarified and couples should undergo counselling with geneticists with respect to the etiology and the potential risks of using retrieved testicular spermatozoa for ICSI.

**References**


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Froland A, Skakkebaek NE. Dimorphism in sex chromatin pattern of Sertoli cells in adults with Klinefelter’s syndrome and couples should undergo counselling with geneticists with respect to the etiology and the potential risks of using retrieved testicular spermatozoa for ICSI.


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Non-mosaic Klinefelter syndrome


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