Men with Klinefelter Syndrome and their Thoughts on Testicular Sperm Extraction

Master’s Thesis

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Abbe Lai

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ABSTRACT

Men with Klinefelter Syndrome and their Thoughts on Testicular Sperm Extraction

A thesis presented to the Graduate Program in Genetic Counseling

Graduate School of Arts and Sciences
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Waltham, Massachusetts

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Klinefelter Syndrome (KS) is a sex chromosome abnormality causing a variety of clinical features and infertility. KS occurs when a male individual has an extra X chromosome resulting in a karyotype of 47,XXY. Much research has been done to look at the fertility of men with KS and in the mid-1990s a surgical technique, testicular sperm extraction (TESE), was shown to be effective in preserving the fertility of some men. Less is understood about the experiences of the men who utilize this procedure. The purpose of this study was to explore the experiences of men with KS who have undergone TESE to understand the decision making process and to identify opportunities to support men with KS undergoing this process. Individuals 18 years and older with self-reported KS (n=2) were recruited from an online support network and by word-of-mouth to participate in a semi-structured interview focusing on the feelings about TESE, the challenges they faced with their condition, and the supports they utilized. The main motivation for undergoing TESE was a desire for biological children. Participants reported a number of different challenges including: coping with the clinical features of KS phenotype, acceptance of their infertility after a failed TESE procedure, passing on KS and the need for hormone
supplementation. The supports these men utilized included: parents, a partner, and other non-familial supports, such as physicians and online support groups. None of the men in this study were offered an appointment with a genetic counselor. However, genetic counselors may have a role in the care of a man with KS by helping men with KS through the decision making process to undergo TESE, setting reasonable expectations for the procedure and providing support after the procedure.
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Introduction

Klinefelter Syndrome (KS) is the most common sex chromosome abnormality in men with a prevalence of 1 in 600 newborn males (Aksglæde et. al., 2006). KS occurs when a male has an extra copy of an X chromosome, resulting in a karyotype of 47,XXY. Individuals with KS may not know that they have this condition from birth because an overt phenotype may not be noticed until puberty. Features of KS include: infertility, tall stature, language-based learning disabilities, behavioral problems, gynecomastia, small testes, histological changes to the testis and dysregulated hormone and gonadotropin levels (Westland et. al., 2001; Wikstrom et. al., 2011). Some men with KS can experience difficulty coping with certain findings in KS, which can lead to problems later in life (Boada et al., 2009). Feelings of emasculation and diminished self-esteem are associated with features of KS such as gynecomastia and infertility; and these feelings may have lasting detrimental psychological effects in adulthood (Nuzzi et. al., 2013; Turriff et. al., 2011). Men with KS are susceptible to depressive symptoms and a diminished quality of life (Herlihy et. al., 2011).

The most common issue adult individuals with Klinefelter Syndrome have is that they are infertile (Gies et. al., 2012). The exact mechanism of their infertility is unknown at the current time. However, it is most likely due to some effect the extra X chromosome has on the development and function of germ cells or on the Leydig and Sertoli cells found in the gonads (Aksglæde et. al., 2006). There are significant architectural changes that occur within the testis in Klinefelter males that ultimately lead to a near total or total loss of germ cells and sperm.
production. The Leydig cells, which produce the male hormone testosterone, are increased in size, a reflection of their decreased functional ability. Most men with KS will have low to low-normal testosterone levels. (Aksglæde et. al., 2006).

In the early to mid-1990s, it was realized that individual spermatozoa could be retrieved from the testes of some men with sperm production failure and that those sperm, when used in conjunction with assisted reproductive technologies (ART), could fertilize an egg, create an embryo, and lead to term delivery of a healthy infant (Schoysman et al., 1993; Oates et. al., 1997). The process of sperm retrieval or testicular sperm extraction (TESE), involves a surgical removal of a part of the testicle, which is then analyzed for mature spermatozoa (Rajfer 2006). Tournaye and colleagues (1996) applied this technique to Klinefelter men and found mature sperm while Palermo and colleagues (1998) documented the first pregnancy using surgically harvested sperm from a 47,XXY male. Since that time, numerous publications have documented successful sperm retrieval rates of 50-60% in azoospermic men with 47,XXY (Madureira et. al., 2014).

There are risks associated with the TESE surgical procedure. One side effect of the procedure is a decline in serum testosterone, which may or may not recover fully in 12-19 months post-operation. This decrease in serum testosterone may warrant the need for testosterone supplementation. The study by Haliloglu and colleagues (2013) showed a decrease in serum testosterone after the procedure, for all individuals. Testicular atrophy and hypogonadism have also been reported but are much less common (Haliloglu et. al., 2013).

One study done by Madureira and colleagues (2014) looked at the clinical outcomes for 65 individuals who underwent TESE. The researchers used a conservative open testicular biopsy with spermatic cord block technique, where fragments of the testicle were removed in multiple
procedures to try and preserve hormone levels. Spermatozoa was recovered in 25 of 65 patients, but this study did not find correlations between successful sperm extraction with age, testicular volume, serum FSH/LH, testosterone, number of testicular fragments analyzed, or time it took to complete extraction of the same. Nineteen of these patients used fresh sperm and ICSI was done immediately and twelve clinical pregnancies were achieved resulting in ten deliveries, twelve newborns and two clinical abortions. Five individuals chose cryopreservation and went through ICSI at a later time, resulting in four clinical pregnancies and five newborns. This study reports that frozen-thawed testicular spermatozoa had poorer fertilization rates, lower-grade embryos and pregnancies in later cycles. The seventeen newborns had no apparent malformations and there was no early neonatal death. Additionally, aneuploidy screening of all these children reported no abnormalities in chromosomes 13, 18, 21, X or Y. This study provides further evidence that men with KS can have healthy children with a normal number of chromosomes.

However, it raised a concern: why is TESE unsuccessful in such a large proportion of men with KS and what are their fertility options (Madureira et. al., 2014)?

The large percentage of individuals with KS who undergo TESE unsuccessfully is a big issue. To try and remedy this, Haliloglu and colleagues (2013) looked at whether it would be worth repeating TESE if a primary extraction has failed. This study looked at 18 men with KS, mean age 30.3y, who have had an unsuccessful micro TESE. A repeated micro TESE was performed on each of these individuals. Three of these men had a subsequent successful sperm retrieval after the first failure, and one of the men went on to have a healthy child from sperm retrieval during the repeat TESE. The option of a second TESE may be successful for some individuals so it is an option open to individuals who are willing to try again, despite the low success rate (Haliloglu et. al., 2013).
Some other possibilities for individuals who had an unsuccessful primary TESE are adoption, use of a sperm donor or, in the near future, potentially for maturation of spermatogonia that may be present within their testicular tissue. One study by Van Sean et. al. (2012) looked at samples from 24 individuals who had no sperm recovery with TESE. The immunohistochemical marker, MAGE-A4, which is expressed in primary spermatocytes, was used to detect the presence of spermatogonia. Four individuals had a positive screen and this was confirmed again by vimentin staining (Van Saen et. al., 2012). These individuals may benefit from in vitro maturation of spermatogonia which has been shown to be successful by Zhu and colleagues (1997). Thus, adults with KS can be subdivided into three groups: those showing mature sperm, those with spermatogonia, and those were germ cells cannot be recovered. Those who have no detectable germ cells still have the option of adoption or the use of a sperm donor (Van Saen et. al., 2012).

Very little research about how individuals with KS feel about TESE-ICSI has been done. Only one study, Maiburg and colleagues (2011) looked at attitudes towards TESE-ICSI by individuals with Klinefelter syndrome. In this study, 90% of men with KS wanted children at some point in their lives, 44% of KS men reported that a life without children would be less valuable compared to one with children, 41% of men with KS reported that the maximum 25% priori chance of pregnancy rate is good, and 75% of men with KS reported they would probably opt for TESE-ICSI (Maiburg et. al., 2011). A limitation to this study was that men were not asked if they had already gone through TESE else ware, but since 75% of men reported they would opt for it in the future, we assume they have not. Nothing has been reported about how individuals feel after going through the procedure, which is important because many individuals do not have a successful extraction. This study sought to fill this gap by directly speaking to men
with KS about their thoughts after having gone through the TESE procedure to see if this population could be better served by the inclusion of genetic counselors to the list of existing care providers they see.
Methods

Brandeis University’s Institutional Review Board approved this study.

Study Population

Participants were recruited through the Association for X and Y Chromosome Variations (AXYS), an online support network, using a website posting and email distribution list. Recruitment materials encouraged interested individuals to email the student researcher directly. Additionally, we attempted to recruit using snowball-sampling techniques; at the end of our interviews, we asked each participant to mention the study to other men he knew with KS who have gone through TESE. We completed an eligibility assessment by phone for each potential participant. To participate in the study, men had to: be at least 18 years of age, speak fluent English, have a self-reported diagnosis of non-mosaic Klinefelter syndrome, and have undergone a testicular sperm extraction procedure. Once the student researcher determined an individual was eligible, she emailed an information document for the participant to read. We scheduled time for the participant and the student researcher to go over the information sheet together and obtain verbal consent before the interview began. We offered each participant a $25 gift card as a token of appreciation for their time.

Interviews

We used a qualitative study design to allow for flexibility throughout the interview, which aided with data collection and provided a way to identify themes through in-depth analysis. We designed a semi-structured interview guide with 10 open-ended questions (Appendix A). The three areas of focus in the interview guide were: 1) Feelings about TESE
before the procedure 2) What supports were available during the process 3) Questions about the overall procedure and the feelings afterwards. The same interview guide was used for each participant, but the specifics of the questions depended on the issues that arose. Following the recorded section, which included questions in the three areas, we gathered demographic information on each participant and recorded this by hand, to further protect patient identity, when sending the interview recordings for transcription.

Data management and Analysis

We conducted and recorded all interviews through freeconferencecalling.com or freeconferencecall.com. We then sent each interview recording to a professional confidential transcription company and received back a written transcription of each interview. To ensure the privacy of the participants, we de-identified the transcripts, and assigned each one a code number. Recordings and transcripts were stored on box.com which is a storage cloud which meets Brandeis University’s security expectations. We analyzed our data using ATLAS.ti (version 7.5.10) software. We coded information from the transcripts to condense the data into analyzable units. We assigned codes to sections of texts and paragraphs based on important and interesting findings that we noted in the transcripts. We further categorized the codes into code families, and then into broader themes.
Results

Characteristics of Study Population

Five men contacted us expressing their interest in the study. Two of the men never responded after the initial contact. One man had not yet undergone a TESE so did not meet eligibility criteria. Only two men completed the study. The interviews lasted 45 and 49 minutes. All participants were willing to share information about their lives with KS and experiences they had with TESE. Both of the men identified as Caucasian. Participant 001 is from the United States and was diagnosed with KS due to primary infertility work up in his twenties. Participant 002 is from Australia, and was diagnosed with KS at age 19 following a work-up for gynecomastia. Both these men saw specialists for their TESE and had the procedure done as an adult. Table 1 displays information about the participant's demographics.

Table 1: Demographic information of the participants

<table>
<thead>
<tr>
<th></th>
<th>Participant 001</th>
<th>Participant 002</th>
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</thead>
<tbody>
<tr>
<td>Current Age</td>
<td>46y</td>
<td>66y</td>
</tr>
<tr>
<td>Karyotype</td>
<td>47, XXY</td>
<td>47, XXY</td>
</tr>
<tr>
<td>Education level</td>
<td>Associate's Degree</td>
<td>High School</td>
</tr>
<tr>
<td>How were they diagnosed</td>
<td>Fertility work up</td>
<td>Gynecomastia</td>
</tr>
<tr>
<td>Age at extraction</td>
<td>31y</td>
<td>19y</td>
</tr>
<tr>
<td>Current marital Status</td>
<td>Married</td>
<td>Single</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian</td>
<td>Caucasian</td>
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*Themes*

Four major themes arose from the data: Why men with KS seek TESE, challenges/considerations, supports, options after an unsuccessful extraction. Each theme was further subdivided into sub themes (see Table 2).

Table 2: Summary of areas of discussion topics, themes and subthemes

<table>
<thead>
<tr>
<th>Discussion topics</th>
<th>Theme</th>
<th>Subtheme</th>
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<tbody>
<tr>
<td>Feelings about TESE before the procedure</td>
<td>Why men with KS seek TESE</td>
<td>The desire to have biological children</td>
</tr>
<tr>
<td>The challenges and supports</td>
<td>Challenges/ considerations</td>
<td>KS Phenotype</td>
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<td></td>
<td></td>
<td>Infertility</td>
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<td></td>
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<td>Passing on KS</td>
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<td></td>
<td></td>
<td>Hormone supplementation</td>
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<tr>
<td>Important supports</td>
<td>Supportive parents</td>
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<td></td>
<td>A supportive partner</td>
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<tr>
<td>Questions about the overall procedure and the feelings afterwards</td>
<td>What options are available when the extraction is unsuccessful</td>
<td>Pregnancy options</td>
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<td></td>
<td></td>
<td>No decisional regret</td>
</tr>
</tbody>
</table>

1. *Feelings about TESE before the procedure*

   The participants all had some phenotype consistent with KS. This phenotype is what led them to a diagnosis of KS as adults. For both of these men, they recalled that all family planning options (adoption, sperm extraction and use of a sperm donor) were presented.
Why men with KS seek TESE

a. *The desire to have biological children*

The first topic that this study provides insight on is the driving factor behind why men choose to do TESE. Both men arrived at their decision to undergo TESE because this procedure is the only way for these men to have biological children. Both participants shared their desire to have children that are biologically related to them and their partner. Participant 001 was married and pursuing fertility options with his wife when he had the TESE procedure. He chose TESE to move forward with the goal of having a biologic child that was unfortunately unsuccessful. He mentioned:

"that was my only chance to have a child, and I had to work that out, and at that point – like I said, we did that, and then they said there wasn’t any chance, and then at that point I had to pretty much figure out what was my next move, because, “What are we going to do?”"

Even though Participant 002 was unmarried at the time he underwent the procedure, he also expressed the hope for biological children in the future. Thus, he consented to having a biopsy on both testicles to check for fertility at the same time as he was going in to have gynecomastia surgical correction.

"Well, I think I wanted children, not I probably wanted children, I wanted children, but all it was just like a, what would you say, it just went along with the thing, like he was finding out whether I could have children or not. He was-- Well, he had to get rid of the gynecomastia lumps on me first, so they decided to do the biopsy at the same time as the breast removal, and that’s how it happened."

2. *The supports and challenges during the process*

Challenges and important considerations

a. *The KS phenotype*

As mentioned above, men with KS can have a constellation of features that may be difficult to cope with. Both men mentioned how the size and consistency of their testicles were
an issue for them. Participant 001 had a constant pain in his testicles, which he also reported being smaller:

"One issue that I already deal with anyway, and I never really understood it until – I don’t know – in the last 10-15 years, or whatever – is I always had like a slight testicular pain, because they’re about the size of – like very small tiny peanuts. There’s nothing to my testicles, so they’re abnormally shaped, and that’s all part of the condition."

Participant 002 did not mention having any pain with his testicles but he reported they were also small and firm. He also reported having gynecomastia and having those removed was a priority for him:

"he also tested my, or felt my testes to see how big they were, etc. and found that they were small and hard. And of course he also had a look at my breasts, which had like a hardening underneath the nipple. It was actually bigger, the nipple. They were about as big as kneecaps and as hard under each nipple. And basically it was fatty tissue which they removed."

b. Infertility

Both of these men were diagnosed with KS and upon examination were diagnosed infertile. This was difficult for the men to cope with since they both wanted to have biological children. Participant 001 mentioned feelings of stress after finding out that the TESE was unsuccessful; he turned to professional assistance to help him cope with his fertility situation:

"And so, when I found out about this, the first blow, and it was really hard, and I had to see a psychologist, and a psychiatrist, and just to deal with the fact that I couldn’t have kids."

Participant 002 also recalled the disappointment at finding out that he wouldn’t be able to have biologic children, but did not utilize any professional assistance to help him cope:

"But in actual fact what they were telling me, there was no hope, but at my age at the time and my, I really wanted to have kids later on in life, so I figured it was probably a bit of wishful thinking, I think, but I was pretty upset that I couldn’t be a father, or I may not be able to father children one day."
c. Passing on KS

All men and women are able to have children affected with Klinefelter Syndrome or another sex chromosome aneuploidy. At the time of their procedures, the thought was that the incidence may have been higher for men with KS to have a child with a sex chromosome aneuploidy syndrome (Foresta et al., 1999). Participant 001 mentioned being made aware of this possibility by the fertility clinic but did not let it affect his decision to pursue TESE:

“But thinking about, “Hey, I’m going to pass this on.” If we have a boy. It’s like, “Oh, my gosh.” I didn’t even think about that end of things. But my aunt eased things off my mind, and I said, “You know what? I’m doing it because I had no issue with that.”"

Participant 002 also made a reference to this possibility and that it may affect some people differently:

"Who knows? It’s one of those things where the mothers are taking it on board, because I think they feel guilty that they have raised a son who has got Klinefelter’s and he might not even care."

d. Hormone supplementation

Testosterone levels may decrease after a TESE procedure so having hormone screening regularly is very important before and after the procedure to check if hormone supplementation is necessary (Haliloglu et. al., 2013). Both men met regularly with an endocrinologist to have their hormone levels assessed and were put on testosterone after the procedures at the recommendation of their endocrinologists. Participant 001 was thirty-one years old when he started supplementing testosterone, while participant 002 was nineteen years old. Participant 001 mentioned feeling angry that his low testosterone was not caught earlier in his life because he blames that for some of his other health problems, which may or may not be related.
Important supports during and after the process.

There are many considerations that must be taken into account when deciding to undergo TESE. Listed above are only a few of the challenges the participants were faced with. Some of these considerations are difficult to cope with and require external support to handle. The participants identified some resources that helped them cope with many of the difficulties they faced. Some of the resources include support from the family, support from medical professionals and utilizing support groups.

a. Supportive parents

Both participants expressed how supportive their parents was about the TESE. Both men were diagnosed with KS and had TESE done at very different stages of their adult life; but they both expressed how the support from their parents was important in helping not only with the cost of the procedure but also for emotional and mental support as well:

Participant 001: "We weren’t rich at that time, and nobody covers that kind of stuff, even now, for healthy people, money-wise, so my dad had said whatever it costs he’ll help pay for that in order for me to have kids."

Participant 002: "they were supportive. But I came from a very, I suppose, loving family where they supported me, and when I was . . . when I had the operation. I remember my father drove my mother and my brother down to see me"

b. A supportive partner

Both participants mentioned how a supportive partner was very important for them. Participant 001 was actively trying to have children with his wife when he was diagnosed infertile, and he expressed how important it was to have a partner that accepted him during this time:

"I’m lucky to have a woman like that that puts up with me, and all my strange, and health issues, and etc."
Participant 002 wasn’t married when he had his procedure and found out he would most likely not be able to have children. However, he recalls telling his wife before they got married and mentioned that she had just accepted and was willing to try other avenues for pregnancy if it didn’t work out:

"Like I said, that was, the official result was 0.05% chance of ever having a baby, or making a baby, more to the point. And I actually got married when I was 25, and I had told my wife-to-be that there was a pretty good chance that I couldn’t make a baby."

c. Other supports

There are a variety of people who may be utilized as valuable supports for individuals with KS at each stage of their life. Participant 002 expressed how one particular endocrinologist has been a big help to him throughout his life and has been seeing him for the last 40 years:

"I was just going to say one of the doctors that I was seeing at the time, an endocrinologist, I still see him today, would you believe. I have been seeing him all these years. He is 67 and he is starting to slow down now, but that’s incredible. He had just finished his internship when I came along."

Participant 001 found solstices through support groups and connecting with someone who was more experienced for guidance:

"And I found a guy on a support group back in – like I said – the prehistoric age of computers, and he kind of helped me through some of the understanding of what this was, and what it meant, and why."

3. Questions about the overall procedure and the feelings afterwards.

Both participants did not have a successful extraction and decided to go try other avenues to have children. The participants were both ultimately able to have children and were generally content with the entire process.
What options are available when the extraction is unsuccessful

a. Donor sperm

Since both men did not have a successful sperm extraction, they were left with two options to have children: adoption or use of a donor sperm. This decision was very individualized to each person; however, ultimately, both participants had children with the aid of a sperm donor. Participant 001 had stressed a strong desire to have a biologic child of his own. When that was deemed to no longer be an option, he and his wife chose to explore the option of IVF using donor sperm. He explained the reasoning behind his decision:

"… and my thought about going with donor sperm was at least there’s two things that were taken care of: My wife can obviously have a child, and number two, it’s part my wife’s genetics, and that’s the greatest part, because at least it’s a part of her that my daughter has."

Participant 002 and his wife, however, were more open to exploring all of their options. He described looking into both a sperm donor program and an adoption center:

"We actually went through a sperm donor program. . . And we put in our names for adoption. We had a letter, or a phone call from adoption people saying that they have got a baby for us, and also the IVF people ringed us up that we were next to come in."

Ultimately, his wife ended up pregnant by another man (unbeknownst to the participant at the time) so they did not have to utilize either of these options.

b. Content with results of their decision

Both men became fathers and expressed that they would not have done things much differently, since their course is what ultimately led them to become fathers:

Participant 001: "With everything that happened, and you mean everything? Yeah. I’d go through all this again, and really in all honesty, if I really thought about it, even though they say every child is like $180,000 in the end, which is nothing, when I look at it, really. But yes, I would have done everything the same way, if not much different. Maybe I would have done more research at that time."
Participant 002: "I don’t really think I had a choice. It was just something that happened. Nothing upset me, apart from not being able to father children, but it was just one of those things in life...But anyway, that’s pretty much how it all come to be that I’m glad I’ve got a daughter. I just got her in a different way than most people do."

Based on the information gathered from our review of the literature, as well as from the experiences of the men interviewed, we created a pamphlet on TESE. This pamphlet, geared towards men with KS, aims to provide a balanced perspective of the issues one should consider when thinking about pursuing TESE. The pamphlet includes a brief overview of Klinefelter Syndrome, information about fertility in XXY, options for family planning, information about what a TESE is, and advice gathered from the participants of the study. This pamphlet will be made available to the public on the AXYS website.(see Appendix 5)
Discussion

This study serves as an initial explorations of the experiences of men with KS and the issues surrounding their TESE procedure. What emerged from this study is that men with KS generally want to have children, much like their peers. There are some challenges that men with KS will face when considering TESE as a method to achieve fertility with a partner, but there are supports available to help with these challenges. We also learned more about what some people with KS who have an unsuccessful sperm extraction decide to do and their reactions to those decisions.

1) Feelings about TESE before the procedure

It became apparent after our discussion with Participant 002, that he did not have a testicular sperm extraction but had rather had a biopsy done to test the histological changes of the testicle to see if he would be able to father children. We included him in the study because he self-identified as having underwent TESE, and from the patient point-of-view a testicular biopsy is very similar to TESE because the information that is given is the same: what are the chances that the individual will be able to have biological children.

The primary reason the men with KS in this study pursued TESE was due to a desire to have biological children. This is in line with previous research looking at the motivations for why men would choose to undergo TESE (Maiburg et. al 2011). Maiburg and colleagues (2011) found that while most men understood the risks and limitations of TESE, they opted to pursue TESE because the prospect of having biological children was so important to them.
Adult men with KS are generally seen in endocrinology or urology clinics. Urologists have long been able to handle the clinical manifestations of KS and male infertility independently. However, a multidisciplinary team that also includes a genetic counselor might be useful to men with KS. A genetic counselor may be able to help men with KS at many stages of the TESE decision-making process by helping them set realistic goals for the procedure, understand how they might feel depending on the outcome of the procedure, and explore additional options if the extraction is a success or a failure. Genetic counselors are able to do this because they are trained in interpreting the entire male and female partners’ family history and are experts in helping individuals make informed decisions through a shared decision making process (McCoy, 2000). According to a study by Glyn and colleagues (2012), people tend to appreciate this way of making medical decisions and genetic counselors are trained in this education method so would be an excellent resource at this stage of decision making (Glyn et al., 2012).

2) What were the challenges faced and the supports utilized

We also learned more information on what challenges men were faced with when deciding to do TESE and what supports were available and utilized to deal with these challenges.

Challenges/ Considerations

The subthemes identified in the challenges/ considerations included difficulties coping with: KS phenotype, infertility, passing on KS and the need for hormone supplementation.

The first subtheme identified in this section is men with KS can struggle with the KS phenotype. Both the men in the study expressed some difficulty with the features of KS they displayed, which is consistent with previous literature in the area. The small firm testes, which both participant were affected by, are a very common feature of KS and are often a cause of
issue for many men. Small testicles due to testicular atrophy can cause feelings of emasculation and affect sexuality in men with KS, which can ultimately lead to depressive symptoms and diminished self-esteem (Kvale & Fisherman 1965; Simm & Zacharin 2006). This diminished self-esteem can cause men with KS to have difficulty attaining and maintaining relationships, which can prove to be a barrier to attaining a high quality of life (Herlihy et. al., 2011; Kvale & Fisherman 1965). Additionally, Participant 001 mentioned his testes caused him occasional pain, a source of difficulty and frustration for him. Participant 002’s largest clinical concern was his gynecomastia that he reported needed to be surgically removed when he was 19 years old. Having gynecomastia during adolescence can often lead to psychological distress (Nuzzi et. al., 2013). Even though Participant 002 did not mention specifically any negative feelings about having gynecomastia; based on his testimonial on the importance of having them removed it is reasonable to infer that he may have had some negative associations with his gynecomastia.

The next subtheme identified is men with KS struggled to cope with their infertility. Both participants felt disappointed to find out that they would most likely not be able to have biological children. The idea of the importance of having biological children is not unique to men with KS. The whole infertility population, both men and women struggle with what to do in the face of infertility because the desire to have children is strong for many people (Collins et al. 1992). Infertility often does have a great impact on men. Men with infertility can have depression, increased anxiety, decreased sense of self-esteem and sexuality due to a perceived loss of masculinity caused by their inability to have children (Turriff et. al., 2011; Kvale & Fisherman 1965). However, the symptoms of men with infertility can be less obvious because men tend to be less open about their feelings, stemming from the idea that men need to appear stronger and that the existing support network they have may not appreciate the emotional
impact infertility has on them (Collins et al. 1992; Malik & Coulson 2008). Participant 002’s method of handling the infertility news is consistent with this idea that men may not be comfortable showing the impact of infertility due to a need to appear strong. However, he was younger and single at the time of his procedure, so the impact of his inability to have children might have been less at that time.

The next subtheme identified was the possibility of passing on KS to any male offspring the individual with KS would have. Both men reported that this was a concern to them and at the time of their procedure, it may have been. In the early days of TESE, it was believed that sperm from men with KS would have a higher frequency of being disomic (24, XY or 24,XX). This lead to the belief that individuals with KS would be at an increased risk of having children with 47,XXY or 47,XXX aneuploidy (Foresta et. al., 1999). However, more recently research has disproved this theory. Many TESE procedures have been performed and the resulting offspring have almost all been chromosomally normal (Levon et al., 2000; Ozveri et al., 2015). Some men may have some sex chromosomally abnormal sperm collected but the incidence of this is not believed to be significantly increased above the general population (Ozveri et al., 2015). Genetic counselors and urologists could work together when meeting with men with KS to dispel this myth and make sure the patient has the correct information when making the decision about TESE.

The final subtheme identified in this portion of the study was the need for hormone supplementation for some men with KS, either before or after their sperm extraction. Both participants were placed on testosterone supplementation shortly after their TESE or biopsy; however, both the men were at different stages of their life and at different ages. The process to determine if and when someone needs testosterone supplementation is highly individualized and
is a matter of debate. Some medical professionals believe that all men with KS need hormone supplementation while others are more conservative and believe only boys who need help virilizing at puberty need it (Mehta & Paduch, 2012). What is not contested is the fact that some individuals who were not on hormone supplementation may need hormone therapy after the procedure. Removing a part of the testes is a traumatic event for the testes, which always causes a decrease in serum testosterone after the TESE procedure. Some men may still have enough serum testosterone after the procedure to not need hormone supplementation but others may need testosterone after the procedure because the hormone levels have decreased too much (Haliloglu et. al., 2013).

In addition, the practice of doing a TESE on adolescents is a controversial and highly debated topic. Testosterone supplementation is known to have a detrimental impact on testicular functioning and decreases sperm production. Thus, for the boys who need testosterone supplementation at a younger age they may wish to consider having TESE done while they are adolescents and have any sperm cryopreserved for the future (Mehta & Paduch 2012). However, this practice is not for everyone and boys who are on testosterone supplementation can still have mature sperm found later in life (Mehta et al., 2013). All of these aspects of hormone supplementation must be taken into account for each individual and so it is vital to have a relationship with an Endocrinologist who is familiar with Klinefelter Syndrome.

Supports

The subthemes identified under the theme of supports include: supportive parents, a supportive partner and other non-familial supports.

Having supportive parents was an integral support for both Participant 001 and Participant 002. Both these individuals had the surgery done when they were adults and could
legally make their own medical decisions. Even so, having their parents on board was a great help both financially and emotionally.

A solid relationship with an accepting partner was also an important support for these men. Participant 001 was with his wife at the time he was diagnosed with KS and infertility, and he mentioned on multiple occasions that having a person accept him and be with him through the challenges was a great help. Participant 002 was not with his wife at the time of his extraction and met her later in life. However, once he revealed to her that he was most likely not going to be able to have children and she accepted it, this was a great relief for him. The emotional support from a partner is very important to maintain a healthy relationship. Stressful situations are a strain in any relationship and infertility is a very stressful challenge. The emotional support a partner provides by simply being present is essential in keeping a relationship together (Antonia et al., 1995). Going through TESE and having a child through assisted reproductive technology can often be financially and emotionally burdensome but, as proven by previous research, having a supportive partner during this time that is accepting of their need for ART or is open to alternative methods of starting a family was helpful for both participants.

The next subtheme identified was the non-familial supports that were very helpful for the participants, which included: a urologist, an endocrinologist, mental health professionals and support groups. Having a relationship with a urologist may be helpful for some individuals because they will be the ones doing the TESE procedure and following up after the procedure. Both Participant 001 and Participant 002 stressed the need for an endocrinologist who understands KS. It is a known fact that individuals with Klinefelter Syndrome benefit from regular screening through an endocrinologist because they have unique hormonal requirements for the maintenance of their health (Mehta & Paduch, 2012). When the hormone levels are not
regulated and monitored well an individual's health may suffer and can cause lasting health complications including: depression, loss of muscle tone, decreased energy and decreased libido (Mehta & Paduch, 2012). Participant 002 found this absolutely essential and is lucky to have found and built a good relationship with endocrinologist who has been following him for the last 40 years. Participant 001 was not so lucky, but stressed the need for a good endocrinologist as early as possible because he suffers from some medical complications which he believes may be attributed to his lack of sufficient testosterone for many years.

Individuals with KS may also benefit from the utilization of mental health services. Individuals with KS are at an increased risk to develop self-esteem and depression issues due to a feelings of insufficiency, body image issues, and emasculation (Boada et al., 2009; Malik et. al., 2008; Nuzzi et al., 2013). Participant 001 utilized a therapist to help him with the psychological stress that occurred after his diagnosis with KS and infertility. He also found support groups very helpful because asking questions of other men with KS who have gone through the procedure was therapeutic for him. Shared experiences are a source of comfort for people and men with KS are no exception (Malik & Coulson 2008). An online forum exclusive to men who have undergone a TESE has not yet been established. However, a forum for men with general infertility does exist and has proved to be effective in allowing men with infertility to share their experiences with other men (Malik & Coulson 2008). A similar KS-specific online forum to discuss TESE may prove to be effective for men with KS to serve as a place for guidance and advice from people who have gone through it on what was helpful for them.

A resource that was not mentioned but one that could still be useful is the service of a genetic counselor. None of the participants in this study utilized a genetic counselor because at the time of the Participant 001's TESE and Participant 002's biopsy genetic counselors had not
established a role in the fertility setting. However, today the role of genetic counselors is more widespread and a specialty in fertility and fertility preservation is being recognized as an appropriate setting for genetic counselors (Campbell, 2013). The complex decision making process can be intimidating for medical professionals and patients because as this study demonstrates there are many challenges and considerations that need to be taken into account. Genetic counselors are trained in education and decision-making assistance and would function very well as a part of a team of medical professionals who provide care to individuals with KS (Elwyn et al., 2000).

3) Questions about the overall procedure and the feelings afterwards.

Options after an unsuccessful extraction

Even though both men did not have the same procedure done they were both left with the same pregnancy options: adoption or donor sperm. This decision was unique to each participant. Both participants went through a fertility clinic to order donor sperm. Participant 001 felt adoption was not right for him and his wife, and decided that given any child fathered with donor sperm will still have half his wife's genetics was reason enough to proceed. The selection process for Participant 001 and his wife was carefully considered and very individualized, allowing them to choose a donor with similar physical characteristics in an effort for him to feel closer with the resulting child. This process would differ for each person so deciding which fertility clinic to use is an important decision. When Participant 002 was ready to have children, him and his wife decided adoption and donor sperm were reasonable options, so they signed up for both. Ultimately, adoption and the sperm donor program were not utilized because his wife got pregnant with another man, which he saw as a nontraditional sperm donor. Both adoption and the use of a sperm donor are valid options for family planning, so it is important for couples affected
with KS to be presented with all options so they can weight their preferences and choose the option that is best for them.

*No decisional regret*

The process these men went through was unique to each of them. The ultimate procedure they went through was tailored according to what was available at the time and the decisions they made after was what was best for each of them at that time. Both of them did not express any decisional regret about having the procedure; for them, the discomfort they experienced was worth it because they both wanted children and wanted to know their chances. The success rate for TESE is limited, but for these men, any hope was better than none. Some men may not want to go through with this procedure after knowing any of the challenges these men faced and that is understandable. For these men, the procedures they went through were in some ways a success because it ultimately left a lasting impression and it did lead to them being able to have children, just in a different way than most. The knowledge that they were unable to produce viable sperm, was useful because they were then able to pursue other methods of fertility without wondering “what if I could have had a biological child?” which may have led to an increased level of satisfaction with their eventual fertility choices.

*Limitations and Future Research:*

This study is an exploratory qualitative study designed to learn more about the experiences of men with KS who have gone through TESE. This analysis focused on data from a small sample size (n=2) from a self-selected group of men. All participants identified as Caucasians and all had their testicular sperm extractions and biopsies done more than ten years ago. Given that we were asking participants to report on things that happened years ago, there is a strong potential for recall bias. Additionally, the men in our study had their procedures
performed in different countries, so their experiences may be inherently different. Given the small sample size and the self-referring nature of the study, these results cannot be generalized to all men with KS considering TESE.

The sample size was limited. A reason for this may be that the most active members in this group are parents of newly diagnosed kids and men who have gone through TESE may not frequent the website as often. Additionally, this study did not include any men who had a successful TESE, which may be due to the idea that men who have had a successful extraction may not feel the need to be a part of a support group anymore since they were able to have biological children. Also, we relied on the internet for most of our recruitment and communication with potential participants, which may have limited participation to only individuals who were able to use technology enough to enroll.

There are many areas of interest in this field that could still be studied. Expanding this study to a larger population of men with KS, or to populations with other genetic forms of infertility would be useful. It would be valuable to capture the experiences of men whose TESE was successful, as well as those who have had failed TESE procedures. Additionally, it might be useful to explore the opinions of men who chose not to pursue TESE to learn more about their decision making process and whether they experienced any regrets. However, for any future research of this nature, it is necessary to find a method to better engage the patient population. It may be more effective to work with physicians directly involved with TESE, to directly contact potentially eligible patients who have recently undergone the procedure, instead of relying on an online support group or self-selecting method. Additionally, since some men may not be comfortable being interviewed given the personal nature of the questions, an anonymous survey-type study may yield greater results.
An area of great debate right now is the procedure of TESE on adolescents with KS and freezing their sperm for use later. Many individuals believe this is a great benefit to preserve their fertility since it is known that during puberty an accelerated depletion of germ cells takes place (Wikstrom et al., 2004). However, others argue that sperm retrieval rates might be better in adults rather than children so it would be more beneficially to wait until adulthood to perform the procedure when the child is old enough to consent (Katz et al., 2015). Future research aimed at understanding the decision making process and experiences of adolescents with KS and/or their parents about TESE is warranted.


Appendix 1: Letter of Permission

January 24, 2016

Abbe Lai
415 South St.
MS 116
Bernstein-Marcus Room 121
Waltham, MA 02454

Ms. Lai:

AXYS is pleased to support recruitment for your research study, "Men with Klinefelter Syndrome and Their Opinions on Testicular Sperm Extraction".

Our recruitment support consists of:
- Dedicated space on our research page: [http://www.genetic.org/Action/CurrremResearch.aspx](http://www.genetic.org/Action/CurrremResearch.aspx)
- Associated social media posts on Facebook and Twitter including placement in no fewer than 7 closed Facebook groups.
- Personal appeals to leading medical professionals who specialize in assisted fertility asking them to direct their patients to the study.

We routinely support studies by reissuing outreach messages as requested by investigators.

If you have any questions, please contact me.

James Moore
Executive Director
AXYS
[www.genetic.org](http://www.genetic.org)
303-400-9040
jmoore@genetic.org

AXYS (formerly known as Klinefelter Syndrome & Associates – KS&A), is a 501(c)(3) non-profit organization whose mission is to help individuals with one or more extra X and/or Y chromosomes and their families lead fuller and more productive lives.

The XXXY Project is a project of AXYS.

AXYS • P.O. Box 872 • Pine, CO 80470-0872 • 888-999-9428 • www.genetic.org
Appendix 2: Recruitment Notice

Brandeis University

Are you a man living with Klinefelter syndrome?
Have you had a testicular sperm extraction as an adult?

My name is Abbe Lai and I am a graduate student in the Genetic Counseling Program at Brandeis University. As part of my graduate school training I am conducting a qualitative research project. I am currently seeking volunteers to participate in this project. The goal of this study is to explore the experiences of men who have undergone testicular sperm extraction (TESE) as treatment for their infertility. It is my hope that the knowledge gained from this study will be valuable to other men with Klinefelter Syndrome, genetic counselors and healthcare professionals.
Participations in this study is voluntary and open to men who meet all of the following criteria:
- Have Klinefelter Syndrome
- Are 18 years of age or older
- Have had testicular sperm extraction as an adult
- speak fluent English

Following a brief phone questionnaire to assess eligibility, participants will be asked to take part in one audiotaped telephone interview that will last approximately one 45 minutes. Participants will be given a 25$ gift card to Amazon.com as a token of appreciation for donating their time. All identifying information of participants will be kept confidential and will be destroyed after completion of the study. Identifying details will be changed to protect the privacy of the participants.
If you are interested or you know someone who might be interested in learning more about the study, please email Abbe Lai at al654@brandeis.edu with your name, phone number or email address, and the best time to contact you.

I look forward to hearing from you,
Thank you!

Abbe Lai
al654@brandeis.edu
Genetic Counseling Graduate Student
Brandeis University
Waltham, MA
Appendix 3: Information Sheet

Information Sheet

Purpose of the Study: The aim of the study is to learn more about the experiences of men with Klinefelter Syndrome who have undergone testicular sperm extraction.

Study Procedures:

You will be asked to participate in a recorded phone interview, lasting approximately 45 minutes. You will be asked questions about when and how you decided to undergo this procedure, how you felt about this experience, advice you may have for other men who are in the decision making process and if you received any guidance for the process. You will also be asked specific questions with regard to the procedure and your care surrounding the procedure.

Benefits:

There is no direct benefit to you. We hope that in the future, information obtained from this study will help us gain a better understanding of the experiences of men with Klinefelter Syndrome who have decided to undergo testicular sperm extraction.

Risks:

Your participation in this study presents no more than minimal risk. It is possible that talking about your experiences could cause you distressing thoughts or feelings. If you become uncomfortable, you can skip a question or stop the interview entirely. Should you wish to speak to a professional, Cassandra Buck (cbuck@brandeis.edu) is available to provide additional support and/or resources.

Privacy and Confidentiality:

All records containing identifying information, such as names, email address, telephone numbers, and home or work address will be kept strictly confidential during the study. All study related documents and materials (including eligibility questionnaires, interview transcripts and audiotapes) will be kept in a secure location accessible only to the Principle investigator and student researcher. Transcripts, interview notes, and audiotapes will be labeled with a coded ID number, which will be assigned to you upon enrollment into the study. If you are quoted or referred to in any written or oral reports of this study, you will be given an alternate name. You will never be referred to by
your name or any other identifying information in any written or oral reports based on the interview.

Cost and Compensation:

There will be no cost to you to participate in the study other than the time it takes to conduct this interview. As a token of your appreciation we will send you a $25 Amazon gift card, upon completion of the interview.

Contact Information:

If you have any questions about the study, please contact the student researcher, Abbe Lai at al654@brandeis.edu. If you are having difficulty reaching Abbe Lai, or if you encounter problems related to the study, you may also contact the Principle Investigator for this project, Cassandra Buck, at cbuck@brandeis.edu.

If you have questions about our rights as a research study subject, contact the Brandeis Committee for Protection of Human Subjects by email at irb@brandeis.edu, or by phone at 781-736-8133. We ask that you read the information sheet before the interview. You will be asked if you understood all the information in the information sheet, whether you have any questions, and if you voluntarily agree to participate in this study, before we begin the interview.
Appendix 4: Interview Guide

Introduction

Thank you for agreeing to participate in this interview to discuss your experience with testicular sperm extraction. Your insights on this topic are valuable and we appreciate you sharing your experiences with us. We hope that the information gathered from these interviews can help men thinking about this procedure and healthcare professionals navigate though this decision and understand the implications involved.

Before we begin, I just want to take a minute to review the study. With your permission, I will be audio-taping our interview so that I can focus on our conversation without worrying about missing anything. I will be asking you questions about your experience with and opinions of TESE, as well as some of your supports, specifics about the procedure itself and the results of your extraction. All information we discuss will be kept confidential. This interview will be labeled with only a code to protect your identity and any identifying information will be kept in a separate document. If data from this study is published or presented, your name will never be associated with any of your comments.

I also want to remind you that participation in this interview is voluntarily and if at any time you feel uncomfortable, you may choose to take a break, skip a question or stop the interview. Your participation may not have any direct benefit to you, but we hope that the information we gather will help future men with KS and their health care providers weigh their options when considering TESE.

Before we begin the interview, do you have any questions about the study or your participation?

Do you agree to participate in this study? Do you agree to the interview being recorded?

Okay, great. I’m just going to start the recording, and then we can begin.
Begin audio taping:

Warm up: to begin, I would like to ask you some general, personal questions about your diagnosis of Klinefelter Syndrome.

Feelings about TESE before:

1. What do you remember about when you learned you had Klinefelter Syndrome?
   Age, who told you, was a GC involved, what was your reaction, was TESE mentioned?

2. How did you first hear about testicular sperm extraction?
   What were your reactions upon hearing about this for the first time?
   From who did you hear it from, geneticist, urologist, genetic counselor, Etc?
   What age were you when you first heard about it

Supports:

3. How did you arrive at your decision to do TESE?
   What were your supports at the time?
   What aspects were more difficult what came more easily to you?
   Did any people in particular influence your decision?

4. What was the most difficult part of your journey?
   For example some prompts would be: the surgery itself, the waiting period, the emotional reactions from hearing your results?

5. What have been your supports after your extraction?
   Family, fertility clinic, doctors, support groups, blogs?
   Is there anything that you would find helpful that may have not been provided?

Procedural questions/feelings after:

6. What were the result of your extraction?
What were your decisions upon hearing those results?

When did you start testosterone treatment, if at all?

7. What effect, if any, has this surgery had on your life?

Were you able to have biological children?

Was a donor's sperm used?

Do you see anything differently now that you have gone through this?

8. What are your thoughts about the care you received?

Is there anything you'd like to change?

Was there anything you wish health care professionals would have told you?

9. What are your thoughts and feelings about TESE now?

Is there something you would want other people with KS to know?

Do you have any suggestions for other men and their families going through this?

10. If you could do this all over again, knowing what you know today would you still do it?

*Stop Recording*

Thank you for taking the time to talk to me today, I appreciate it. I have just a few additional questions to ask.

**Demographics**

If you know your karyotype

education level

    high school/ GED, associate's degree, bachelor's degree, master's degree, MD, PHD, other

    current age

Marital status
married, single, in a relationship, other

Race

Caucasian, Black, American Indian, Hispanic, Asian, mixed, other
Appendix 5: Brochure

Purpose
Our mission is to help individuals with one or more extra X chromosome know what some of the options for family planning are.
This brochure is intended to be a starting point to and should be utilized as a guide to promote a conversation with an urologist.

XXY Overview
- Most human cells have 46 chromosomes or 23 pairs of chromosomes.
- Chromosomes are made up of DNA, which are the instructions for how our bodies grow and develop
  - the 23rd pair are the gender chromosomes
  - females have 2 X chromosomes: (46, XX)
  - males have an X and a Y (46, XY)
- Klinefelter syndrome is a condition where a male has an extra X chromosome so instead of (46, XY) they have (46, XXY)
- Individuals with KS may be eligible and benefit from extra services such as:
  - Early Intervention
  - Special Education services
  - Therapy or counseling
  - Testosterone or other hormone treatments
  - Sperm extraction (TESE) combined

Fertility in 47,XXY
- Infertility due to azoospermia, having no detectable sperm in his semen, is the most common issue seen in men with KS.
- Only around 8% of men with KS have sperm in their ejaculate
- The exact cause of the infertility is currently unknown
- Starting from a young age, boys with KS typically have decreased sperm counts
- Around when puberty starts, there is an increased rate of loss of germ cells

Options for family planning
- Adoption
- Sperm donors
- Testicular sperm extraction (TESE) with intracytoplasmic sperm injection (ICSI)
  - Sperm donors and TESE require the use of in vitro fertilization (IVF)
TESE Procedure Overview

- TESE is a surgical procedure where an urologist removes a part of the testicle, in many cases from both testicles.
  - Usually done under general anesthesia
  - Performed through a very small incision
  - Suture will dissolve on their own
- The material that is removed is examined to see if it contains any mature sperm.
- Three possible results of TESE:
  - Mature sperm is present,
  - Spermatogonia or immature sperm is present
  - No germ cells can be recovered
- If mature sperm is found, it can be then used with IVF-RCSI to achieve pregnancy.
  - The sperm can be used right away or cryopreserved (frozen) for use at a later time.
  - Either option can result in children
- Some individuals may choose to have TESE in adolescence and have sperm frozen for later use.
- Results are usually returned the same day.

Who can use this?

- Men who have azoospermia

What to expect after the surgery

- Some pain may be felt after the surgery, but it should be temporary.
  - Rest for one or two days
  - An icepack can help with any pain
- Removing a part of the testicle may reduce the amount of testosterone in the blood, which can cause health complications if untreated, including but not limited to:
  - Low energy
  - Depression
- Typically testosterone levels will be measured before and after the surgery.
  - For some men, hormone replacement (HR) may be needed because the levels have decreased too much.

Success rate

- On average, the chance to have sperm detected is about 50%.
  - The chances to achieve a successful pregnancy are about 25%.
- Many individuals may not have a successful extraction.
  - A second TESE can be considered, but the success rates are much lower than the original.
  - Adoption or sperm donor are still options to have children.

Other considerations

- The chances of passing on KS are about the same as the general population: 1/800 (less than 1%).
- You may still be offered preimplantation genetic diagnosis (PGD), which is a tool that can be used to screen an embryo for extra conditions.

Future prospects

- Spermatozoa, immature sperm, can be matured outside of the body and may be used to achieve pregnancy.

Advice from patients

- Find medical professionals that are familiar with KS, especially an:
  - Endocrinologist
  - Urologist
- Keep up with the regular appointments to check hormone levels.
- A counselor or therapist may help a couple dealing with infertility.
- Reaching out to other men who have gone through it may help.
- You can still have children using a sperm donor or adoption if TESE is unsuccessful.