Towards the responsible clinical implementation of stem cell-based fertility treatments
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CHAPTER 5

PERSPECTIVES OF INFERTILE MEN ON FUTURE STEM CELL TREATMENTS FOR NON-OBSTRUCTIVE AZOOSPERMIA

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**ABSTRACT**

Concerns have been expressed about the rapid introduction of new fertility treatments into clinical practice. Patients’ perspectives on new treatments and their introduction into clinical practice are unexplored. Two alternative treatments for testicular sperm extraction followed by intracytoplasmic sperm injection in men with non-obstructive azoospermia (NOA), the formation of artificial sperm and autotransplantation of in vitro proliferated spermatogonial stem cells, are in a preclinical phase of development. This study aimed to explore, prior to future clinical introduction, which treatment aspects are valued by NOA patients and would be taken into account in deciding to undergo these future treatment options. In-depth telephone interviews were conducted with 14 men with NOA. Interviews were transcribed, analysed with content analysis and data saturation was reached. Besides the obvious factors, success rates and safety, patients valued ‘the intensity of the procedure’, ‘the treatments’ resemblance to natural conception’ and ‘feeling cured’. Patients supported the development of these treatments and were eager to take part if such treatments would become available in the future. The patient’s perspective on innovative treatments can (co)direct reproductive research. More research into the patients’ perspectives on innovations and minimal thresholds to be met prior to their introduction into clinical practice is required.
ABSTRACT

Concerns have been expressed about the rapid introduction of new fertility treatments into clinical practice. Patients' perspectives on new treatments and their introduction into clinical practice are unexplored. Two alternative treatments for testicular sperm extraction followed by intracytoplasmic sperm injection in men with non-obstructive azoospermia (NOA), the formation of artificial sperm and autotransplantation of in vitro proliferated spermatogonial stem cells, are in a preclinical phase of development. This study aimed to explore, prior to future clinical introduction, which treatment aspects are valued by NOA patients and would be taken into account in deciding to undergo these future treatment options.

In-depth telephone interviews were conducted with 14 men with NOA. Interviews were transcribed, analysed with content analysis and data saturation was reached. Beside the obvious factors, success rates and safety, patients valued 'the intensity of the procedure', 'the treatments' resemblance to natural conception' and 'feeling cured'. Patients supported the development of these treatments and were eager to take part if such treatments would become available in the future. The patient's perspective on innovative treatments can (co)direct reproductive research. More research into the patients' perspectives on innovations and minimal thresholds to be met prior to their introduction into clinical practice is required.

INTRODUCTION

The failure to conceive within 1 year of unprotected intercourse is frequently caused by reduced semen quality. In one-third of couples, male subfertility is the only diagnostic feature. Psychosocial research in reproductive medicine has mainly focused on women (e.g. because of cultural associations between reproduction and women), while less attention has been paid to the burden of male infertility and fertility treatment, especially those treatments involving men directly, such as testicular sperm extraction (TESE). Involuntary childlessness affects men's emotional and social wellbeing negatively. Whereas undergoing assisted reproduction treatment initially decreases men's distress levels, their distress increases in case of longer, unsuccessful treatment periods (i.e. longer than 17 months). Men for whom infertility results in childlessness have a decreased quality of life compared with men for whom childlessness is voluntary, which is mainly explained by infertile men's subthreshold levels of depression and anxiety. Besides the effectiveness of fertility care, men value patient centeredness, although they are not willing to trade off the same percentage of pregnancy rate for patient-centred care as are women. Whereas it is known in medicine generally that there are groups of patients who argue for the right to participate in research, both for personal and altruistic reasons, little is known on of the decision process, specific decisive factors and their relative weight in reproductive medicine.

For men faced with non-obstructive azoospermia (NOA), the most severe form of male infertility, the only treatment option for conceiving genetically their own children is TESE with intracytoplasmic sperm injection (ICSI). However, TESE–ICSI has a limited success rate in men with NOA, as the sperm retrieval rate per TESE cycle is 56% and the subsequent live birth rate of ICSI is 41%, resulting in a 23% chance to father a child.

Two alternative treatments for men with NOA are in a preclinical phase of development. First, irrespective of whether germ cells are still present within the testis, 'artificial sperm' can be generated from somatic cells. To create artificial sperm, a patient's somatic cells are transformed into stem cells, either via induced pluripotent stem cells or via somatic cell nuclear transfer in embryonic stem cells of a donor. These stem cells are subsequently induced to differentiate into spermatozoa, which can be used for ICSI. In mice, such artificial sperm has resulted in offspring. In humans, male haploid cells have been formed but no attempts have been made to use these haploid cells to fertilize human oocytes and transfer them to the uterus.
Second, if NOA patients still have functional spermatogonial stem cells (SSCs), autotransplantation of in vitro proliferated SSCs could theoretically restore sperm production (Figure II). After testicular biopsy, SSCs are proliferated in vitro and subsequently transplanted to the testes, where they can migrate to their niche and produce mature spermatozoa. If successful, this approach would theoretically lead to the presence of spermatozoa in the ejaculate hence allowing natural conception. Offspring as a result of transplantation of SSCs have been born in mice, rats, and zebrafish. Survival of in vitro proliferated human SSCs, which have been xenotransplanted to mice, has been reported but no attempts have been made to autotransplant SSCs in humans.

Concerns about the rapid introduction of new fertility treatments into clinical practice, without sufficient effectiveness and safety assessments need to be taken into account. Governance is needed and the conditions that should be met before implementation into daily practice should be carefully defined. It is unclear who should define these conditions. Involving the general population has been suggested, but patients’ perspectives on new fertility treatments and, subsequently, on conditions for their introduction into clinical practice are unexplored. It is relevant to know which treatment aspects are valued by patients.

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**Figure I. The making of artificial sperm followed by ICSI.**

A somatic cell (in this case a fibroblast) is transformed into a stem cell, which is then differentiated into mature sperm cells in vitro. The female partner receives hormone treatment, after which mature oocytes are retrieved from the ovary. The previously generated sperm cells are then used to fertilize the oocyte in vitro. After successful fertilization, the embryo is placed into the uterus to achieve pregnancy.
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Figure II. Autotransplantation of in vitro proliferated spermatogonial stem cells (SSCs).

SSCs are removed from the testes by means of a testicular biopsy, these SSCs are then proliferated in vitro and subsequently transplanted back into the testes. As a result, sperm production in the testes of this patient can increase so that mature spermatozoa can appear in the ejaculate, allowing natural conception.

This study aimed to explore, prior to future clinical introduction, which treatment aspects are valued by patients with NOA and would be taken into account in deciding to undergo these future treatment options.
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MATERIALS AND METHODS

Telephone interviews with men diagnosed with NOA who were scheduled to undergo TESE explored the patients’ perspectives on their current treatment and on the two potential future treatment options. The study was presented to the medical ethics review board of the university clinic but was approved without further extensive review as it was judged non-interventional, in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO).

Recruitment
Subsequent men diagnosed with NOA and scheduled to undergo TESE at the Centre for Reproductive Medicine of the Academic Medical Centre (Amsterdam, The Netherlands) between April 2011 and May 2011 were asked to participate by their clinicians and all gave their written consent for study participation. Participants received written information, including pictograms and text, on the studied treatment options in preparation for the interview. This written information was developed by reproductive biologists and clinicians at the level of understanding of the lay public, for example by using ‘lay terms’ instead of scientific terms.

As is appropriate for qualitative research the number of interviews was defined by data saturation (i.e. when a sense of closure is achieved because no new themes answering the research question emerged in three successive interviews\textsuperscript{283-285}).

Data collection
In-depth telephone interviews of 30–45 min were conducted in June 2011 by a female interviewer (SH), who was familiar with all aspects of the treatment options but not involved in patient care. The semistructured interview guide and a topic list were developed based on both the literature\textsuperscript{273,286-288} and the input of an expert panel, including an embryologist, two gynaecologists and a urologist–andrologist. The interview guide was (pilot) tested with two males not involved in this study and resulted in minor textual adjustments.

At the beginning of and during the interview, the patient’s understanding of the written information on (the mechanisms of) the treatment options was checked (e.g. the consistency between patient’s valuing one treatment over another for feeling cured and actual differences between the two treatments’ abilities to cure); additional explanations were given when needed.

The interviewer first questioned each patient’s perspective on TESE–ICSI and on the two potential future treatment options. Patients were presented with the hypothetical scenario that all three treatment options had equal success rates and risks (as no data are available on the two potential future treatment options) and
were asked to indicate which treatment would be their first and second preferences. These questions were complemented with questions addressing specific treatment aspects from the topic list. The interviewer regularly summarized the patient’s responses to assure accuracy of understanding\textsuperscript{289}. The interviews were recorded digitally. After each interview, the interviewer transcribed the interview and added new themes to the topic list for subsequent interviews.

**Data analysis**

Data were analysed by use of content analysis using constant comparison involving the following consecutive stages: (i) multiple readings (i.e. to grasp the context); (ii) highlighting meaningful units (i.e. patient’s quotes that address the research question); (iii) grouping meaningful units into categories; (iv) comparing meaningful units between categories in order to integrate categories (i.e. constant comparison); (v) delimiting the theory; and (vi) writing the theory\textsuperscript{131-133}. Two researchers (SH and MHM) independently performed the analysis; discrepancies were resolved by discussion.

The data analysis and data collection were intertwined\textsuperscript{290}. Insight from the analysis guided subsequent interviews and, at the same time, the credibility of generated categories was tested\textsuperscript{131,133}. For data presentation, examples of patient quotations were selected, anonymized and translated. Although a realist approach was used to describe patients’ motivations, in the discussion a constructionist perspective was used to elaborate on the provided insight\textsuperscript{291}.

**RESULTS**

**Participants**

Fourteen men diagnosed with NOA and scheduled to undergo TESE were asked to participate and all agreed. Data saturation was reached after 12 interviews and confirmed by the 13th and 14th interviews. The median age of the men was 37 years (range 29–47 years).

**Perspectives on treatment options**

The following five treatment aspects were valued by patients: (i) success rates; (ii) risks of congenital abnormalities; (iii) intensity of the procedure; (iv) resemblance to natural conception; and (v) feeling cured.
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**Success rates**
Most patients indicated that the success rates of treatment options were important to them. However, the success rates were not always dominant in patients’ trade off of all factors influencing their perspective:

“This method [SSC autotransplantation] feels less artificial than method two [artificial sperm], so I would opt for this method regardless the success rates of both” (patient 7).

The perceptions of patients on acceptable success rate differed. For some patients, the ∼25% success rate of TESE–ICSI was the minimal requirement to consider treatment, while others were willing to undergo treatments with lower success rates:

“Right now my chance is and will remain zero, so everything that raises this percentage even slightly would make us happy” (patient 3).

**Risks of congenital abnormalities**
Risks of congenital abnormalities associated with treatments were important but not always dominant to patients. Patients differed in the congenital abnormalities risk rates they considered acceptable. For some patients, minor differences in risks had major implications on treatment choice; for others this was less influential:

“Well, this might sound very selfish, but I do not care that much [about abnormalities in offspring]. I would rather have a child of my own that has an abnormality than to have a child from a sperm donor; I would care less about such a child” (patient 7).

**Intensity of the procedure**
Patients valued a limited ‘intensity of the procedure’. More specifically patients preferred procedures with ‘no or few operations’, ‘the least sensitive biopsy location’, ‘no need for ovarian stimulation and oocyte retrieval for their partner’ and ‘shortest possible time span to get to a live birth’.

In line with these findings, artificial sperm was applauded, as a biopsy in, for example, the arm was considered less troublesome than a testis biopsy. When autotransplantation of in vitro proliferated SSCs was considered, patients shared that the need for two operations (one to extract SSCs and one to autotransplant the in vitro proliferated SSCs) would be compensated by their partners not having to undergo ovarian stimulation and oocyte retrieval:
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Feeling cured

Another aspect that was of importance to patients was the impact of the different treatment methods on their self-esteem. More specifically, SSC autotransplantation, theoretically allowing natural conception in case of success, would make them feel cured and feel better about themselves:

"If I would be making sperm myself again ... yes, then I would feel better" (patient 11).

Asking patients whether they had ethical objections showed that none of the patients had ethical objections against the discussed treatment strategies.

Eagerness to accept new treatment options

Their wish to parent their own genetic child was patients' drive to accept TESE–ICSI and the two alternative treatments:

"We know that it is not going to be a fun experience for either of us [the couple] but what it has to offer outweighs that by far" (patient 1).

Patients were eager to participate in both new treatment options:

"This [autotransplantation of SSCs] is amazing, where can I sign in?!" (patient 1).

Furthermore, all patients indicated to be willing to try multiple treatments in case one of the treatment options failed, as long as they considered themselves young
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enough to become parents. Moreover, many indicated to be willing to accept a number of repercussions (i.e. high risks, low success rates, high burden):

“Even if it would be an operation on my heart, I just want them to find something. It would not matter to me even if it would take ten procedures” (patient 14).

Two patients spontaneously offered to try the new treatments in an experimental setting.

In the hypothetical scenario that all three treatment options would have the same success rates and risks of congenital abnormalities, the majority of the patients (9/14, 64%) chose autotransplantation of SSCs as a first preference. The following interview quotation exemplified patients’ trade off of the valued treatment aspects:

“In principle I think this [SSC autotransplantation] is the perfect method, although it requires two operations. Because you have to let nature take its course and because the woman does not need to have a hormonal treatment and all those things” (patient 4).

TESE–ICSI and artificial sperm were each chosen as a first preference by a minority of patients (3/14, 21% and 2/14, 15%, respectively). As a second preference, patients most commonly preferred TESE–ICSI (9/14, 64%). Although artificial sperm was rarely chosen as a first or second preference, mainly because it seemed ‘unnatural’ to patients, patients did appreciate this option when they understood that from a clinical point of view this was a last-resort option for patients without viable sperm cells or SSCs in their testis.

DISCUSSION

Examining patients’ perspectives on new treatment options, especially prior to their implementation into clinical practice is novel, let alone perspectives of men. Men with NOA are very eager for alternatives to TESE–ICSI and would be prepared to undergo multiple different treatment options. Patients support the development of artificial sperm and autotransplantation of SSCs. This study shows that patients’ perspectives on innovative treatment options are defined by the intensity of the treatment procedure, the resemblance to physiology and the feeling of being cured besides treatment safety and effectiveness.

Critical reflection on the methodology
The qualitative approach was appropriate to generate in-depth understanding of the nearly unexplored male patient’s perspective on reproductive research
The three aspects ensuring trustworthiness of qualitative research – credibility, dependability and transferability – were assured. Credibility was demonstrated by careful selection of exemplifying interview quotations to contextualize the data. Dependability was assured by using a semistructured interview guide and by data analysis by two researchers. Furthermore, data saturation showed that the data remained consistent. To facilitate the readers’ interpretation of the transferability of the findings, insight into the context framing of the participants’ responses was provided by describing the (conditions for and of) data collection and the analysis process. Moreover, interview quotations were provided to enhance the readers’ ability to interpret transferability.

Some critical considerations need to be made. First, only men were questioned on their perspective and preference, although real-life fertility treatment decisions are taken by couples. Second, only men who already agreed to a TESE treatment were questioned. These men are likely to be more motivated for treatment than men not willing to undergo TESE, who might have different perspectives on new treatment options. In addition, despite reaching data saturation, presumably the perspective of men with more exceptional socio-cultural backgrounds (e.g., religion) or of settings (e.g., countries not reimbursing assisted reproduction treatment) is not represented.

**Critical reflection on the findings**

This study shows that many different factors play a role in patients’ choice between specific treatment options and that effectiveness and safety are important to patients but not always dominant in their choices. Male patients’ considerations of effectiveness are in line with their tendency to approach their reproductive choices based on their scientific effectiveness. However as for male patients’ perspectives on care and clinic choice, effectiveness does not dominate patients’ treatment choices because it is traded off for patient centeredness. The finding that treatment safety is not the defining motif in infertile men’s accounts seems to fit with research with subfertile women who consider having a child with a disability as more desirable than having no child at all. The fact that patients differed in the risks and effectiveness they were willing to accept, stresses the importance of patient involvement in decision making.

The desire of male infertile patients to limit the intensity of treatment options is in line with female patients preferring expectant management over intrauterine insemination if pregnancy is guaranteed for both options.

It is not surprising that male infertile patients want to limit their partner’s need for ovarian stimulation and oocyte retrieval by undergoing two testicular biopsies, if possible. It is in line with infertile men feeling helpless when they witness their
partners' treatment burden, their desire to save their partners (emotional) energy, and to be an 'emotional rock' (of support) for their partner. Previous studies on contraception showed that men considered having a vasectomy as an act of masculine responsibility and protection of their more 'fragile' female partners. This concept of masculinity could be viewed in the context of male sex role theory. Hegemonic masculinity in its plural sense is used by contemporary men to construct masculine identities, and includes taking on responsibility, having difficulties talking about emotions, being stoical, being invulnerable and only visiting a doctor when having a legitimate reason to do so. Finally, the previously reported feelings of guilt of male patients could also play a role in their willingness to take over the burden of the treatment.

Attaching value to resemblance to natural conception is in line with previous research in which men stated that IVF is knowable (i.e. easy to understand) and they perceive it to be hardly a technological intervention and merely another way of doing what nature does.

The fact that the men with NOA had no ethical objections against the proposed future treatment options is remarkable in light of resistance of the general public against stem-cell-based technologies. However, opposed to the general public, patients are eager to become a genetic parent and thus have different ends justifying the means of stem cell technologies.

The value attached by men with NOA to feel cured can be explained by the grief experienced by men as a result of an infertility diagnosis and by their gender-specific difficulties with infertility being perceived as a threat to their masculinity.

Male patient's motivation to take part in multiple, even experimental treatment options can be explained by their strong desire to father a child genetically their own. However, longitudinal and theory-led research is still needed to explain (dis)continuation by infertile males in daily practice.

**Implications for research and practice**

It would be interesting to follow up the current exploratory study with a survey including a large cohort of men with NOA and their partners as they will share their actual treatment decision, which will allow the evaluation of the relative value of the identified treatment aspects. Furthermore, the perspective of infertile women on potential treatments involving artificial gametes remains an unexplored field.

The results of the current study endorse research into creating artificial sperm and autotransplantation of in vitro proliferated SSCs. Moreover, they can (co)direct the
focus of this research by taking account of all factors valued by patients besides effectiveness and safety.

This study is informative for the current need for a more conscious implementation of innovations in the field of reproductive medicine by defining minimal thresholds for introducing innovative treatments into daily practice\textsuperscript{16}. From the patient’s perspective, such thresholds should be defined for three treatment aspects, besides effectiveness and safety. The next step is to involve several stakeholders including medical professionals (i.e. those striving to provide beneficence with their treatments), patients (i.e. those who will undergo treatment) and the general public (i.e. those representing the future child) in defining the height of the thresholds.