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ARTICLE

Perspectives of infertile men on future stem cell treatments for nonobstructive azoospermia

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Born 18 November 1991, Saskia Hendriks studied Liberal Arts and Sciences at Amsterdam University College, and received her BSc summa cum laude majoring in biomedical sciences with a minor in international relations and health in 2012. She was awarded the 'Thesis of Distinction' of the University of Amsterdam for her research on artificial gametes. For 2 years, Saskia has been studying patient involvement in the implementation of innovations in the field of reproductive medicine at the Academic Medical Center. Saskia is a PhD student and simultaneously studying for her medical degree. Her research focuses on the biological formation of artificial gametes and the societal and ethical aspects of artificial gametes.

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 nonobstructive 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.

KEYWORDS: artificial gametes, assisted reproductive technologies, male infertility, patient centredness, spermatogonial stem cells, TESE

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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 (Brandes et al., 2010).

Psychosocial research in reproductive medicine has mainly focused on women (e.g. because of cultural associations between reproduction and women; Oudshoorn, 2003; Throsby and Gill, 2004), while less attention has been paid to the burden of male infertility and fertility treatment (Culley et al., 2013; de Jonge, 2013), especially those treatments involving men directly, such as testicular sperm extraction (TESE) (Cousineau and Domar, 2007; Dancet et al., 2010b; Throsby and Gill, 2004). Involuntary childlessness affects men's emotional and social wellbeing negatively (Hadley and Hanley, 2011; Hinton and Miller, 2013; Malik and Coulson, 2008; Meerabeau, 1991; Mikkelsen et al., 2013; Saleh et al., 2003; Throsby and Gill, 2004; Wright et al., 1991). Whereas undergoing assisted reproduction treatment initially decreases men's distress levels (Pook et al., 2002), their distress increases in case of longer, unsuccessful treatment periods (i.e. longer than 17 months; Peronace et al., 2007; Pook and Krause, 2005). Men for whom infertility results in childlessness have a decreased quality of life compared with men for whom childlessness is voluntary (Klemetti et al., 2010), which is mainly explained by infertile men's subthreshold levels of depression and anxiety (Chachamovich et al., 2010). Besides the effectiveness of fertility care, men value patient centredness, although they are not willing to trade off the same percentage of pregnancy rate for patient-centred care as are women (Dancet et al., 2010a,b; van Empel et al., 2011). 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 (Locock and Smith, 2011), little is knowon of the decision process, specific decisive factors and their relative weight in reproductive medicine.

For men faced with nonobstructive 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 (Dabaja and Schlegel, 2013).

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 (**Figure 1**). 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 (Hayashi et al., 2011; Nayernia et al., 2006). 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 (Aflatoonian et al., 2009; Easley et al., 2012; Eguizabal et al., 2011; Kee et al., 2009; Panula et al., 2011; Tilgner et al., 2008; West et al., 2011).

Second, if NOA patients still have functional spermatogonial stem cells (SSCs), autotransplantation of in vitro proliferated SSCs could theoretically restore sperm production (**Figure 2**). 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 (Kanatsu-Shinohara et al., 2011; Kubota et al., 2009; Ohta et al., 2009), rats (Hamra et al., 2005; Ryu et al., 2005; Wu et al., 2009), and zebrafish (Kawasaki et al., 2012). 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 (Sadri-Ardekani et al., 2009, 2011).

Concerns about the rapid introduction of new fertility treatments into clinical practice, without sufficient effectiveness and safety assessments need to be taken into account (Harper et al., 2012; Schatten, 2002; van Steirteghem, 2008; Winston and Hardy, 2002). Governance is needed (Schatten, 2002) and the conditions that should be met before implementation into daily practice should be carefully defined (Harper et al., 2012). It is unclear who should define these conditions. Involving the general population has been suggested (Brezis et al., 2011), 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 prior to the introduction of new treatments into clinical practice. First, patients codefine the relevance of developing new treatments, as they are the ones choosing whether or not to undergo treatment. Second, meeting treatment aspects valued by patients, also referred to as patient centredness, is a central aspect of the quality of any given treatment.

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.

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 noninterventional, 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)