Towards the responsible clinical implementation of stem cell-based fertility treatments
Hendriks, S.

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CHAPTER 10

GENERAL DISCUSSION AND IMPLICATIONS FOR FUTURE RESEARCH
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This PhD-project was initiated in 2012 based on a call for a debate on the responsible clinical implementation of stem cell-based fertility treatments\textsuperscript{30-32}.

Currently, stem cell-based treatments are still in a preclinical stage of development. Our systematic review published in 2015 revealed five in vitro and four in vivo approaches to generate stem cell-based sperm or oocytes, which rely on variable sources of stem cells (i.e. germline stem cells, embryonic stem cells and induced pluripotent stem cells; \textit{chapter II}). Of the nine identified approaches, seven had already led to the birth of offspring in animal models and five to the generation of sperm or oocytes in humans. Since then, several of these findings have been replicated and further developed (e.g.\textsuperscript{256,257}). Although these recent developments may shorten the time to clinical implementation, important data on functionality, safety and efficiency of (human) stem cell-based gametes is required\textsuperscript{218,219}.

\section*{REFLECTION ON FINDINGS}

This PhD-project added new insights to the worldwide literature on the responsible clinical implementation of stem cell-based fertility treatments regarding four topics: \textit{‘indications’, ‘treatment characteristics’, ‘societal consequences’, and ‘decision-makers’}. As such, it covers most of the topics that have recently been flagged for consideration in a report of the Dutch Center of Ethics and Health to the Ministry of Public Health, Well-being and Sports\textsuperscript{543}.

\subsection*{Indications}

Our systematic review identified several potential indications for using stem cell-based fertility treatments (\textit{chapter III}). Professionals assumed in their opinion papers that the general public would be unlikely to support stem cell-based fertility treatments for the less traditional indications\textsuperscript{135,165}. We were the first to actually question the general public and found that the majority of the Dutch general public would accept stem cell-based fertility treatments for all indications except for female infertility in heterosexual couples in which the woman is of post-menopausal age (acceptance rate 17\%) or for fertile women who want a child that is genetically only her own (acceptance rate 27\%) (\textit{chapter IV}). Previous studies questioning the acceptability of other types of medically assisted reproduction (e.g. through donor gametes, adoption) found similar acceptability rates per indication\textsuperscript{28,221-224,235-241,244,245,248}. The similar acceptability rates per indication of stem cell-based fertility treatments and other types of medically assisted reproduction was surprising as stem cell-based fertility treatments are in principle more interventional and less conventional. Furthermore, they would drastically
extent the biological boundaries of reproduction, and in general therapies using stem cells are not widely accepted among the general public\textsuperscript{246,299,329}.

Similar to the ‘off-label’ application of IVF and other fertility treatments, i.e. for other indications than the one for which the treatment was originally designed, stem cell-based fertility treatments may also be used by couples who do have alternative options available for achieving genetic parenthood, such as couples with unexplained infertility. Interestingly, the acceptability of the use of stem cell-based fertility treatments for the indication unexplained subfertility, was low among gynaecologists but high among the general public (43\% versus 82\%, \textit{chapter IV}). This difference between gynaecologists and the public may incite questioning with regard to the classical medical framework of only treating diagnosed physical conditions. If patients and society do not feel strongly about maintaining this strict medical framework, should we continue to uphold it?

\textbf{Treatment characteristics}

Our studies showed that more treatment characteristics than the classical safety, effectiveness, burden, and out-of-pocket costs\textsuperscript{303} were valued when considering to opt for (patients) or offer (gynaecologists) stem cell-based fertility treatments (\textit{chapter V, VI, and VIII}). The following additional treatment characteristics played a role: (i) genetic parenthood, (ii) curing infertility, (iii) conceiving at home, (iv) resemblance to natural conception, (v) technological sophistication, (vi) costs covered by the national health care system, (vii) diagnostic value and (viii) the acceptability of treatment’s broader implications (\textit{chapter III, VI, and VIII}).

Comparing the importance attributed to all these characteristics by patients and gynaecologists in our studies (\textit{chapter V, VI, and VIII}) and in other studies\textsuperscript{293,294,318-322,381,383,497,516-522}, led to the identification of the six most important treatment characteristics: child health, costs covered by national health insurance, maternal health, pregnancy rate, genetic parenthood, and curing infertility. We found that, when modelled together, all these treatment characteristics influenced the treatment preference of patients except for genetic parenthood (\textit{chapter VIII}). The treatment preference of gynaecologists was influenced by all treatment characteristics but curing infertility and genetic parenthood had the least influence (\textit{chapter VIII}).

Child health had previously been reported to be important to patients\textsuperscript{544}, and gynaecologists\textsuperscript{37,38,545}. Our insight that it is the treatment characteristic with the largest effect on treatment preferences of patients and gynaecologists (\textit{chapter VII, chapter VIII}) is surprising as except for one study\textsuperscript{16} previous studies did not rank child health among the most important characteristics\textsuperscript{293,294,319,516-520}. These previous studies, however, questioned the importance of child health risks due to
multiple pregnancies, whereas we questioned the importance child health risks with respect to major congenital abnormalities. In our view, the presence of major congenital abnormalities better reflects child health as multiple pregnancies may or may not result in child health problems and might also have the positive connotation of having two children instead of one child. Our data on the importance of child health to patients may relieve concerns about infertile patients’ limited ability to take account of the interests of their child\textsuperscript{546}, as intended parents apparently already put the health of their children first.

The importance of the costs of reproductive medicine covered by national health insurance to gynaecologists or patients had not been examined previously. Our finding that costs covered by national health insurance are important to gynaecologists is in line with these costs defining whether physicians from other fields order diagnostic tests or prescribe medications\textsuperscript{547}. Our finding that costs covered by national health insurance influence infertile patients’ treatment preference is novel (\textit{chapter VIII}). It is not likely to reflect that assisted reproduction should be paid out-of-pocket, as over 85% of patients and gynaecologists in Germany support reproductive medicine to be covered by national health care insurance\textsuperscript{324}. Rather, this finding suggests that, at least in the Netherlands and Belgium, informing patients on treatment costs covered by national health insurance may limit healthcare expenditure. According to physicians, patients carry responsibility for reducing healthcare costs\textsuperscript{548}. Patients, however, may not wish to be informed on treatment costs\textsuperscript{549}.

The importance of maternal safety of reproductive medicine to gynaecologists had not been questioned previously. For patients, previous findings on the importance of the same risks (e.g. OHSS, multiples) were contradictory\textsuperscript{319,321,381,383,517-520,522}. We found that child health was more important than maternal health to patients and gynaecologists (\textit{chapter VIII}). In patients, this might be seen in the context of all aspiring parents accepting the maternal risks of carrying a pregnancy for the prospect of becoming parents. In gynaecologists, this is more surprising as maternal health is generally prioritized in obstetrics (e.g. inducing preterm birth for preeclampsia\textsuperscript{550}).

Previous studies reported genetic parenthood to be important to patients\textsuperscript{344} and to gynaecologists\textsuperscript{340}, however the motivations for valuing genetic parenthood remained unclear. Chapter V confirmed that virtually all patients prefer genetic over non-genetic parenthood. Besides certain parenthood goals that inherently rely on parents having a genetic tie with their offspring, genetic parenthood was often considered required for fulfilling general motivations for parenthood. The importance of genetic parenthood relative to other treatment characteristics had not been studied previously among patients or gynaecologists. However, clinical
decision-making of patients and gynaecologists, resulting in donor gametes only being used in <10% of fertility treatment cycles\textsuperscript{339}, would suggest genetic parenthood to be a priority to patients and gynaecologists and would outweigh other treatment characteristics such as effectiveness. Exemplary for this is the dominant use of TESE-ICSI as first line treatment in couples with non-obstructive azoosperma. TESE followed by three cycles of ICSI has an overall 29% chance of achieving a live birth while the use of donor sperm for twelve months in these same couples results in a 59% chance of live birth\textsuperscript{280,500,501}. In practise, most couples only use donor insemination after TESE-ICSI has failed. It was therefore surprising to find that when taken into account together with other treatment characteristics, genetic parenthood did not affect the treatment preference of patients, and only had limited effect on gynaecologists’ preferences (chapter VIII). This discrepancy between clinical practice and the preferences of patients and gynaecologists in our study might be explained by patients and gynaecologists making ‘autopilot’ decisions instead of explicitly weighing all treatment characteristics\textsuperscript{351,355} or societial pressure to first use all available technologies resulting in genetic parenthood\textsuperscript{502}. Our insight also challenges the extent to which genetic parenthood can be used to advocate for the development of stem cell-based fertility treatments. Genetic parenthood is important to patients and gynaecologists but the demand for novel treatments among informed patients and gynaecologists might be limited as the advantage of genetic parenthood is only worth a limited amount of additional risks, lower pregnancy rate and higher costs.

Pregnancy rates were previously reported as crucial to treatment choice of patients\textsuperscript{293,294,318-321,497,517-522} and gynaecologists\textsuperscript{277}. We confirmed that pregnancy rates were important to patients and gynaecologists (chapter V, VI, and VIII). However, instead of being crucial in determining treatment choice, pregnancy rates only had the fourth largest effect on treatment preferences in our study involving men and women with severe infertility (chapter VIII). This may be explained by these previous studies not comparing pregnancy rates to the same other treatment characteristics (e.g. they omitted costs covered by national health insurance, and child health was only assessed relating to multiples).

All current treatments are aimed at circumventing infertility to achieve a single pregnancy, and hence cure involuntary childlessness rather than curing infertility. The possibility of auto-transplanting germline stem cells as a form of stem cell-based fertility treatments would in theory allow curing infertility as this would, for example, result in regaining the lifelong ability to produce spermatozoa. Although raised as important by both patients and gynaecologists (chapter V, VI, VIII), it only significantly affected treatment preference for patients (chapter VIII). Furthermore, the underlying reasons for its importance appeared to differ (chapter V, VI, and VIII). Interviews with gynaecologists revealed they valued curability out of principle
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since this is the goal of medicine, and because this would allow couples to conceive at home instead of in the hospital (chapter VIII). Patients’ rationales, however, more often referred to being able to have multiple children after being cured from infertility and to preventing the psychosocial burden of carrying the diagnosis of infertility (chapter V and IV).

Societal consequences
Our review of professionals’ opinion papers identified a wide range of consequences of the clinical implementation of stem cell-based fertility treatments (chapter III). In chapter IX, we showed that at least one out of ten members of each of the three questioned stakeholder groups valued each of the potential negative and positive health and societal consequences of stem cell-based fertility treatments. This finding supports the previous request for regulators to weigh all potential negative and positive health and societal consequences of novel medical techniques.$^{529,533,540,541,551-553}$

Decision-makers
The need to regulate the clinical implementation of stem cell-based fertility treatments had not been studied previously. However, various professionals have proposed regulating the clinical implementation of different kinds of novel reproductive techniques.$^{11,17,37,528}$ We found that a large majority of three stakeholder groups (>85%) was in favour of regulating at least one potential negative consequence of the clinical implementation of stem cell-based fertility treatments (chapter IX). Thereby, they support creating a regulatory committee for the clinical implementation of stem cell-based fertility treatments.

The regulatory body most frequently supported by all three questioned stakeholder groups was a national bioethics committee (chapter IX). A bioethics committee being preferred as the regulatory body rather than a medical professional association, is in line with medical doctors not being experts on the societal consequences of fertility treatments and with fear for medical doctors’ potential over-eagerness to treat or have personal interests in offering treatment.$^{16,21,25,36}$ Furthermore, a bioethics committee as the regulatory body for clinical implementation corresponds to national or institutional (ethical/review) committees for clinical research which are already in place.$^{7-9}$

The outcome that almost all questioned gynaecologists, patients and members of the general public agreed that regulatory decisions should be taken after consulting with advisors from various backgrounds (chapter IX) is in line with findings from a study on priority setting in health care.$^{536}$, as well as the underlying principles of this thesis. The fact that, besides bioethicists, gynaecologists were the most popular advisors, is in line with a medical professional association being
named as advisors for other health care decisions, such as the allocation of health care resources.536,539,554.

REFLECTION ON METHODOLOGY

Our approach to study the perspective of gynaecologists, patients and the general public to enable thorough reflection on the responsible implementation of novel reproductive techniques has thus far only been used by the Human Fertilisation and Embryology Authority (HFEA) in the United Kingdom. More specifically, the HFEA consulted with multiple stakeholders on the clinical implementation of mitochondrial transfer555. Opinion leaders are also advocating for stakeholder consultations on germline genome editing556-561.

Our thorough and stepwise approach of studying the conditions for responsible clinical implementation included (i) identification of all potential indications, treatment characteristics and societal consequences that should be taken into account; and (ii) assessing their importance and acceptability through questioning multiple stakeholders. We identified all potential indications and all positive and negative consequences named in the debate on stem cell-based fertility treatments by performing a systematic literature review of opinion papers (chapter III). We made sure that all treatment characteristics were named by interviewing until data saturation was achieved (chapter V, chapter VIII). Next, we included all identified aspects in our questionnaires (chapter IV, chapter VI-IX), resulting in questionnaires with complete and non-directive preparatory information and questions. Our final survey was presented to a multidisciplinary independent expert panel, which checked for non-directive phrasing (chapter IV, chapter IX525,226).

Of course, any scientific approach carries flaws or drawbacks that have to be taken into account to evaluate the contribution of the work. We mention six critical considerations on our methodology.

First, whether gynaecologists, patients and the general public were the most appropriate stakeholders can be questioned. We selected gynaecologists because of their professional expertise, responsibility for treatment outcomes and role in day-to-day decision-making on the clinical application of (new) treatments11,22,34,35. Physicians in general might however not be able to form a morally sound opinion because they may have a well-intended over-eagerness to treat, a self-interest in offering treatment, and debateable qualifications for deciding on the social implications of treatments, as suggested in our interviews with gynaecologists (chapter VIII) as well as in previous studies16,21,33,36. We selected patients because they are directly faced with the consequences of infertility and its treatments, and
as they are the legal representatives of the future child. Patients might however, not be able to form a morally sound opinion because they are in a vulnerable position and as they may, as beneficiaries, be more willing to take risks and to shift moral boundaries. We selected the general public because they may be affected by the broader societal impact of fertility treatments and because learning about their values fits the moral and legal principles of a democracy. The general public may however not be able to form a morally sound opinion because they lack the necessary knowledge to allow sound reasoning. According to gynaecologists, patients and the general public, especially bioethicists, psychologists, and/or the government should be questioned (chapter IX). Noticeably, there was, among our questioned stakeholder groups, only limited support (12-18%) for the regulatory body to consult with the general public. There was more support for the regulatory body to be informed on physicians’ (92-73%) and patients’ (29-72%) perspectives.

Second, we mainly report on the perspective of the majority of each stakeholder group and this is not per definition the morally right perspective. Our insights can, however, inspire the normative reflection of e.g. the regulatory committee. The balance between following the democratic majority versus what is morally right is a subject of its own.

Third, the legitimacy of the gathered answers of our stakeholders stands or falls with their understanding of the proposed scenario and question. In our qualitative studies (chapter V, chapter VIII), we checked the understanding of our interviewees. We could not do this in our surveys (chapters IV, chapters VI-IX) and therefore our questionnaires were developed thoroughly and piloted in cognitive interviews among members of the general public until proven feasible.

Fourth, besides explorative qualitative research (chapter V, chapter VIII) we mainly studied the perspectives of stakeholders with the aid of questionnaires. Research comparing the effect of this methodology as compared to individual or focus group discussions is limited and conflicting. Questionnaires result in instinctive responses, which might result in a more ‘valid’ representation of actual societal values. As compared to focus groups, questionnaires as well as individual interviews, enable individual consultation, which reduces susceptibility to normative social influence and prevents groupthink. Questionnaires, however, do allow less time than individual or focus group interviews and allow no peer discussion as focus group interviews do, which helps stakeholders to form an opinion. Taking it one step further than focus group interviews, deliberative forums of public engagement such as citizen juries, would allow participants to spend multiple days deliberating, questioning experts and framing the outcomes. This elaborate time consuming and expensive process of deliberation with multiple stakeholders does,
however, relinquish the participants’ representativeness of their respective stakeholder groups.

Fifth, whether the timing of this PhD-thesis is optimal could be questioned as stem cell-based fertility treatments are still in a preclinical stage of development. In our view, performing our studies now, rather than once the treatments are already upon us, allows for responsible clinical implementation. However, at the same time, crucial information for determining the acceptability of stem cell-based fertility treatments is currently still missing, such as pregnancy rates and safety risks. We therefore informed the participants on these uncertainties and asked them to make specific assumptions (e.g. chapter IX). Furthermore, we, in this context, refrained from inquiring directly whether stem cell-based fertility treatments should be introduced, as conclusions may incite decision-making that, despite availability of new data, may be difficult to adjust. Noticeably, though further data from preclinical studies may increase consensus on the desirability of stem cell-based fertility treatments, differences in perspectives will likely remain considering our pluralist society with different interests of different stakeholder groups.

Sixth, the transferability of our findings to different cultures and over time is doubtful. The acceptability of reproductive technologies is related to ethnic background and may change over time.

**IMPLICATIONS FOR CLINICAL PRACTICE**

Stem cell-based fertility treatments are still in a preclinical stage of development and as important treatment characteristics, like safety, are still unknown, we cannot yet take a responsible decision on their future clinical implementation. This PhD-thesis, however, has other direct implications for daily fertility clinic practice. Our studies may improve the understanding of fertility clinic staff about the variety of fertility treatment characteristics valued by patients. These treatment characteristics likely apply to all fertility treatments and not only to stem cell based fertility treatments. Fertility staff can use this in-depth understanding to develop information on treatments and to reach shared treatment decision-making. A very clear example is that this PhD-thesis showed that fertility staff should not expect patients to have such a strong preference for genetic parenthood that they do not want to consider using donor gametes early on in their treatment trajectory (chapter VII). Fertility patients proved to be willing to give up genetic parenthood in return for increased safety and cost-effectiveness (chapter VIII). In addition, the overview of possible motivations for preferring genetic parenthood may facilitate shared decision-making (chapter VII). Finally, the general public’s support for using stem cell-based fertility treatments for non-traditional indications may support
fertility staff offering currently available fertility treatments to these intended parents.

IMPLICATIONS FOR FURTHER RESEARCH

As with any question, our primary questions generated more questions than answers.

The review of the biological progress into the development of stem cell-based fertility treatments revealed that more preclinical research is required to develop and assess safe, effective, and cost-efficient stem cell-based fertility treatments. Our findings may help prioritizing preclinical research questions and research goals. For example, genetic parenthood is only worth an 18 percent reduction in pregnancy rates. If subsequent studies suggest meeting these conditions is unlikely, limited use of stem cell-based fertility treatments may be expected. This has implications for the proportionality of resources spent on the development of these treatments. Still, it does not imply that research into clinical applications of stem cell-based fertility treatments should be halted. As with rare diseases, small groups of potential beneficiaries may still legitimize developing these novel treatments. Whether they will be widely adopted remains to be seen.

One topic that requires further study is the importance of genetic parenthood. First, it would be interesting to test the relative value of genetic parenthood throughout the treatment trajectory in different patient groups. These groups could include patients with less severe types of infertility, as well as intended parents with genetic mutations that are pursuing preimplantation genetic diagnosis (PGD) to prevent transmitting these mutations to their offspring. Testing whether our findings on hypothetical treatment choices after being informed on the six key treatment characteristics also apply to actual treatment choices if informed on the six key treatment characteristics would also be of value. Finally, for establishing the true benefits of genetic parenthood, it would be interesting to prospectively study the effect of a genetic tie on couples’ ability to attain all their motivations for parenthood.

Several identified potential consequences may benefit from further exploration. For one, the likeliness of certain consequences to occur may require further analysis and/or modelling. For example, it has been argued that stem cell-based fertility treatments will have a significant effect on population size (which was assessed both positively, in the context of shrinking population sizes in Western societies, as negatively, in relation to global issues of overpopulation). Whether indeed the numbers of intended parents that would potentially be treated with stem cell-based
fertility treatments could result in population-level effects may be modelled. For other identified consequences, normative reflection of the results may provide additional insights on their validity. For example, the slippery slope argument has been flagged as a logical fallacy.

Future studies on the acceptability of stem cell-based fertility treatments may focus on the perspectives of additional stakeholders that should be consulted according to a majority of one or more of our stakeholder groups, including bioethicists, psychologists, and policy-makers (chapter IX).

Studying perspectives of stakeholders from different cultures and/or countries may be informative.

This thesis focused on the implications of creating gametes from stem cells for fertility treatments, whereas other applications are possible and deserve further scrutiny. For one, generating gametes from stem cells could benefit science\textsuperscript{219}. Furthermore, the generation of stem cell-derived gametes may be applied to clinical genetics, in addition to reproductive medicine. Intended parents with genetic mutations wishing to prevent transmitting these mutations to their offspring can currently use preimplantation genetic diagnosis. This entails using in vitro fertilization to generate multiple embryos that are tested for the genetic mutation after which only non-affected embryos are used to attempt to establish a pregnancy. Currently, the success rates of this technique are highly limited by the number of oocytes, and thus embryos obtained. Furthermore, intended mothers are exposed to the risks associated with an IVF procedure. Creating oocytes from stem cells may be used to generate an unlimited pool to select embryo’s using preimplantation genetic diagnosis. This would circumvent IVF-associated risks for intended mothers, and increase success rates, thereby dramatically increasing the number of medical conditions/desired characteristics for which using this technique may be a worthwhile endeavour. This may have large scale effects on future generations\textsuperscript{219}. Finally, further research should compare findings between different methods of studying stakeholder perspectives (questionnaires, individual or focus group interviews or more deliberative methods) as many have hypothesized on the advantage of each methods, but as empirical data is limited and contradicting\textsuperscript{564}. In addition, studying the impact of preparatory study information and of recent media attention on participants’ response may be relevant.
IMPLICATIONS FOR HEALTH CARE POLICY

Our results call for (Dutch) policy-makers to set up a national bioethics committee to regulate the clinical implementation of stem cell-based fertility treatments. This national bioethics committee should weigh all identified treatment characteristics and societal consequences, and should consult various advisory groups.

Designing a responsible process for the clinical implementation of new techniques is not only relevant for reproductive medicine but for all fields of medicine. In this light, stem cell-based fertility treatments can be considered as an interesting case study given its wide range of consequences. Just like we did for stem cell-based fertility treatments, we would recommend a structured process preparing for responsible clinical implementation for all other novel medical techniques with large-scale societal consequences. This includes, first, identifying all potential indications, treatment characteristics, and societal consequences, that should be taken into account through literature review and qualitative interviews. Second, it includes assessing their importance and acceptability through questioning multiple stakeholders. Differentiating between innovative techniques that require an extensive implementation process versus novel techniques that are merely variations on standard practice was reported feasible in surgery576.

Furthermore, the decision-making process on the eventual clinical implementation of novel techniques needs to be addressed in more areas of medicine. Many professionals have plead for regulating the clinical implementation of novel techniques11,12,14,17,525,527,528. However, the appropriate process to set up this regulation remains unclear, whilst some authors stressed that current regulatory pathways are too slow to respond to the rapid therapeutic developments577. An appropriate process of decision-making is especially important considering that even in case of thorough preparatory preclinical and clinical studies, decision-making on clinical implementation will often have to be made in the absence of complete certainty regarding the outcomes and consequences of the use of the specific intervention. For example, the number of patients that need to be treated to detect an effect and/or the lead time for certain long-term consequences to appear (e.g. development of cancer later in life) may extent the duration of clinical trials, and therefore the time period a treatment is considered experimental. In other areas of society, decision-making under uncertainty has been well-embedded. For example, a judge or jury needs to reach a verdict without absolute certainty on whether the defendant is guilty of the charge. Therefore, a process has been set up, including for example a trial and availability of a defence attorney, that allows society to support the justice system. For eventual errors, a process for follow-up has been designed (e.g. the option of lodging an appeal). Similarly, we would suggest to develop a decision-making process to regulate the clinical
implementation of novel technologies that society can support. This may also include follow-up systems that require setting up registries to monitor potential long-term consequences of novel technologies. The results of our studies (*chapter IX*) and those of others may aid in designing this process. Still, designing and installing such regulatory processes will likely require a shared effort of government and various stakeholders.

Finally, throughout the process of introducing novel techniques, providing the public and other stakeholders with appropriate information is crucial and may require joint efforts and even renegotiating roles and responsibilities of scientists, policy-makers and journalists.