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ARTICLE

Follow-up in the field of reproductive medicine: an ethical exploration

BIOGRAPHY

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KEY MESSAGE

Follow-up of children conceived through medically assisted reproduction (MAR) should be an integral part of introducing new reproductive technologies. This requires active involvement of families whose children were conceived through MAR and may hamper responsible follow-up research. Professionals may encourage such families to partake in follow-up research.

ABSTRACT

Research question: What ethical implications, issues and concerns play a role in conducting follow-up studies of children born after assisted reproductive technologies (ART)?

Design: Literature study and relevant experiences of academic medical centres in Brussels, Belgium, and Maastricht, the Netherlands were used to identify and analyse the most pertinent ethical implications, issues and concerns.

Results: According to recommendations from the European Society of Human Reproduction and Embryology, follow-up (ideally long term) of children conceived through medically assisted reproduction (MAR) should be an integral part of introducing new ART. With potentially risky new ART on the horizon, these recommendations need to be taken more seriously. Apart from practical barriers, such as funding, challenges for follow-up include securing active involvement of families of children conceived through MAR, starting with parents of young children, and ideally involving consenting adolescents and adults during a large part of their lives, possibly even into the next generation.

Conclusions: From an ethical viewpoint, the most pertinent issues include the proportionality of the inevitable burdens and risks for families of children conceived through MAR, and the implications of the principle of respect for autonomy. The proportionality requirement is most critical when it concerns incompetent children, who should not be included in research with more than minimal burdens and risks if there is no reasonable expectation of benefit for themselves. With respect for autonomy, we argue that, when seeking voluntary consent for participating in follow-up studies that meet the condition of proportionality, professionals may encourage members of families of children conceived through MAR to partake in follow-up research.

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KEYWORDS

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INTRODUCTION

More than 10 years ago, the European Society of Human Reproduction and Embryology (ESHRE) proposed an ideal research trajectory for evaluating the safety of new assisted reproductive technologies (ART), consisting of pre-clinical research, clinical studies and follow-up (*Pennings et al., 2007*). With potentially risky new ART on the horizon, such as germline gene editing or the use of stem cell derived gametes, and with long-term safety data still being scarce even for existing ART, this approach is increasingly seen as essential to responsible innovation in the field of medically assisted reproduction (MAR) (*Van Steirteghem, 2008*; *Harper et al., 2012*; *Provoost et al., 2014*).

In this paper, we focus on the last step in ESHRE's recommended research trajectory: follow-up studies. Despite a consensus on the importance of follow-up, only a few centres conduct it. Practical and ethical concerns may hamper follow-up being carried out responsibly. Without the illusion of being exhaustive, we explore some of the most important ethical implications, issues and concerns relating to follow-up studies of children born after ART, taking into account the relevant experiences of academic medical centres in Brussels (Free University), Belgium, and Maastricht, the Netherlands.

In the next two sections we chart the envisioned benefits of MAR follow-up for its various stakeholders, describe the types of procedures involved and compare current practice against ESHRE's normative framework recommending follow-up as a part of responsible innovation in MAR. In the second part of the paper, we discuss proportionality and respect for autonomy as the two main ethical issues relevant for responsibly conducting follow-up.

BACKGROUND

Follow-up research in health care and medicine concerns the monitoring of health of patients over time after treatment. In the case of assisted reproduction, participants of such monitoring are not just patients (as for instance in the large number of studies that have been conducted to clarify whether hormonal stimulation puts women at a higher cancer risk later in their lives) but, importantly, also the resulting offspring. Follow-up of the latter is discussed in this paper.

Follow-up studies (both short- and long-term) of children conceived after assisted reproduction generate health-impact data that may be important for four different groups of individual stakeholders, as well as for society at large. First, follow-up may benefit children born via the very procedures under evaluation. This is the case when health problems or health risks are found to be associated either with the use of a specific ART or its use in a specific population, and that allow for timely treatment or prevention. For example, the inheritance of infertility is not yet fully understood. Should an increased risk for premature menopause, for example, be found in girls conceived through MAR in a specific population, preventive actions might be taken, such as oocyte vitrification to expand their reproductive options. Follow-up studies revealing conditions or health risks that are 'actionable' in the sense of allowing for timely treatment or prevention can form the basis of professional guidelines for screening or monitoring the children to whom this may apply.

Second, long-term follow-up becomes transgenerational when the health of the descendants of children conceived through MAR are analysed. Any actionable findings entail that the benefits of follow-up extend to those in this further generation, most of whom will themselves be conceived without medical help. The importance of transgenerational follow-up is widely acknowledged in relation to deliberate interference of ART with the human germline (*Watts et al., 2012*; *National Academies of Sciences, Engeneering and Medicine, 2016*). It also seems important for ARTs more generally, given that possible epigenetic effects may affect next generations.

Third, findings that are used to make MAR procedures safer will benefit future children by reducing their chances of being born or having to live with ART-related malformations or disorders. Obviously, the parents and families of those children will also benefit from such adapted procedures. For example, research has shown that multiple pregnancies are associated with a higher rate of prematurity and low birth weight, which puts children at significant risk of adverse health effects (*Lu et al., 2013*). Therefore, ESHRE recommends single embryo transfer to avoid multiple pregnancies and advises not to transfer more than two embryos per cycle (*De los Santos et al., 2016*). Another example is the observation of a higher risk of malformations in children resulting from IVF involving oocytes with cytoplasmic smooth endoplasmic reticulum aggregates. In 2011, this finding led to the so-called Istanbul Consensus, which recommended that those oocytes should not be used in IVF (*Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011*). In the light of conflicting evidence and the lack of a causal explanation, it was later advised to take a case by case approach (*ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine, 2017*), with the authors of a recent review recommending a policy of giving embryos derived from oocytes with cytoplasmic smooth endoplasmic reticulum aggregates a lower priority ranking for transfer (*Ferreux et al., 2019*). Although disregarding a small but significant percentage of oocytes that may still lead to healthy children has obvious implications for the success rate of IVF, the latter example is a good illustration of the complex trade-off that may exist between IVF safety and efficiency, and of the importance of conducting follow-up studies aimed at generating high-quality evidence required for sustainable policy decisions. Moreover, the example shows that epistemic uncertainty need not stand in the way of defining precautionary policy responses if more conclusive evidence is lacking (*Jans et al., 2020*).

Finally, follow-up contributes to informed decision making by couples or individuals undergoing MAR, as it enables a better understanding of the balance of benefits and risks of a certain reproductive technique. For example, follow-up of intracytoplasmic sperm injection for male infertility has shown that, compared with young men who were naturally conceived, those born after intracytoplasmic sperm injection had lower scores on sperm concentration, sperm count and sperm motility parameters (*Belva et al., 2016*). Such information is important when counselling couples who are considering

fertility treatment. To make an informed decision, they should be able to weigh up the pros and cons.

For society at large, it is important to consider that children conceived through MAR form an increasingly substantial part of the population, which means that even small MAR-related health risks can have a large effect on public health. For example, multiple studies have suggested that children conceived via MAR have an elevated risk of developing cardiovascular diseases later in life (van *Ceelen et al., 2008*; *Wikstrand et al., 2008*; *Scott et al., 2010*; *Scherrer et al., 2012*). If adapted procedures, i.e. use of different culture media, can reduce those risks, this may have considerable population level benefits in addition to giving individuals conceived via ART healthier lives.

Follow-up of children conceived through MAR entails subjecting them to medical, psychological tests, or both, which may be invasive and are often recurrent. Medical tests can consist of assessment of possible (major or minor) malformations, measuring (birth) weight, growth, hearing, visual acuity, blood pressure and neurological examination, including testing movement, muscle tension, reflexes, large and fine motor skills and hand-eye coordination. These tests are carried out by a paediatrician or another healthcare professional. Also, reviewing the child's personal health record and, where relevant, the child's hospital records is usually part of follow-up. In long-term follow-up that aims to examine long-term treatment effects, medical tests may consist of analysing blood samples or saliva specimen and investigating reproductive health by analysing semen samples or examining female reproductive organs. Psychological tests may include analysing cognitive, motor and language developments, behaviour problems and socioemotional development, and the parent–child relationship (*Zhan et al., 2013*; *Heijligers et al., 2018*). In practice, such tests include IQ tests, interviews and questionnaires.

To make information gained through follow-up available for studies evaluating long-term (transgenerational) consequences, it is recommended that centres facilitate a uniform data collection: a registry (*Provoost et al., 2014*). Such registries 'could help document the risk of different ART for prospective children. Over time, this could provide the required evidence base that would allow regulators, professional societies and individual clinicians to better address the needs and concerns of prospective parents and to improve the risk communication process' (*Roy et al., 2017*). Extensive registries are essential, because associations between aspects of a technique and certain health effects may only come to light much later. For example, documentation of specific embryo culture media is necessary to investigate possible associations between certain culture media and important offspring parameters, such as birth weight (*Zandstra et al., 2015*). Importantly, the value of such registries increases if a good registry of a control population exists.

FOLLOW-UP IN PRACTICE

To what extent is ESHRE's normative framework, specifically recommending follow-up studies, put into practice? Although follow-up is considered an important aspect of the responsible innovation of new reproductive treatments by commentators in the ART field, in practice few centres have experience in this regard (*Brison et al., 2013*; Jans *et al*., 2020). Long-term follow up studies are rare (*Mulder et al., 2018*). Although some centres have contributed to follow-up studies extensively, such as at Brussels Free University Hospital, these centres are still the exception.

In many cases in which follow-up was conducted, studies had considerable methodological limitations (*Sutcliffe and Ludwig, 2007*; *Mulder et al., 2018*). One of the main limitations is the complexity of interpreting the scientific data, caused by using different IVF methods, lack of controls and differences in clinical definitions of outcome measures. Additionally, standard protocols on data collection are lacking, which hampers the collection of uniform data on health effects in children born after MAR (*Mulder et al., 2018*).

Practical difficulties are often cited as a reason behind the lack of (methodologically strong) follow-up research worldwide. Follow-up studies often lack funding, which may affect sample size or may complicate follow-up being conducted at all. Long-term studies are costly, time consuming and often face high drop-out rates or loss to follow-up rates (*Barnhart, 2013*). In many countries, 'basic' scientific funding does not cover funding for follow-up research, and alternative funding is difficult to find. With some notable exceptions, such as Denmark (*Norrman et al., 2020*), governments often refrain from financially supporting fertility centres to carry out minimal follow-up. Participation rates are affected by logistical factors, such as the travel distance to the centre in which measurements are made, especially when families are expected to return every few years, and the time investment this entails for them. A further issue is that not all parents of children conceived via MAR tell their children about how they were conceived, which limits the willingness of families to participate in follow-up research, and also raises privacy issues complicating careful recruitment for such studies (*Soini et al., 2006*).

Apart from possible privacy concerns relating to parental disclosure decisions, other ethical issues, i.e. the need for families of children conceived through MAR to lead normal lives, or the fact that children have not consented to be conceived through MAR, are sometimes raised as a ready and unchecked justification for not having to conduct adequate follow-up.

PROPORTIONALITY

As for all scientific research with human participants, the two main ethical issues relevant to assessing the acceptability of MAR follow-up are proportionality and respect for autonomy. We discuss these aspects in the following sections. The proportionality criterion generally requires that the possible benefits to be obtained from the relevant study clearly outweigh the possible risks and burdens for those asked to participate. Applying this to MAR follow-up, we first consider what possible risks and burdens participation in such research may entail. As a large part of MAR follow-up is research with children, we also need to discuss this in the context of internationally accepted guidance, as more stringent proportionality criteria apply for studies involving minors as research subjects.

Burdens and risks of participating in medically assisted reproduction follow-up studies

As follow-up of children, adolescents or adults born through MAR entails

subjecting them to medical and psychological tests, follow-up is inevitably associated with possible risks and burdens. These depend on the type of medical and psychological tests, their frequency and the overall duration of the follow-up study. Medical tests consisting of non-invasive check-ups, such as measuring weight or blood pressure, pose no risk and burden is minimal. Some tests, however, may be more invasive, e.g. blood drawing and tissue typing, especially when the latter requires a biopsy. Another example is the examination of the normal development of female reproductive organs, which requires a gynaecological examination. Naturally, in all cases, the preferred method for such examinations should be discussed with, and adapted to, the participants.

Follow-up may cause psychological burdens for the children and their families. To have one's reproductive organs investigated and to be asked questions relating to sexual development and behaviour may cause psychological discomfort. Moreover, follow-up consisting of frequent medical visits over a longer period may be psychologically exhausting. Families of children conceived through MAR may prefer to get on with their lives without repeated reminders of a history of infertility treatment. Additionally, children may face psychological burdens from feeling different from other children. Evidence that psychological burdens for children born after MAR are limited, and these studies did not specifically investigate psychological burdens caused by follow-up (*Ponjaert-Kristoffersen et al., 2004*). In addition to the burdens and risks associated with testing procedures, a further possibly harmful effect of participating in MAR follow-up studies is the potential of findings revealing a serious health risk, leading to knowledge that may be experienced by the child and its parents, as casting a shadow over their lives. While this may be outweighed by the benefit of timely intervention in the case of actionable findings, e.g. when a girl is found to be at a high risk of developing hereditary breast or ovarian cancer, this is not the case for non-actionable findings, e.g. a high risk of a neurodegenerative disorder for which no treatment or prevention options exist, i.e. Huntington's disease. Finally, the extent to which participating in follow-up is considered burdensome may differ between families and individuals, and highly specific practical aspects, such as travelling distance and related time investment, should be considered.

Medically assisted reproduction follow-up as research with minors

Follow-up of children born through MAR is mainly research with minors. Although MAR follow-up is ideally long term and will continue into adulthood, this typically extends a research trajectory that starts with including young children. Moreover, where long-term follow-up becomes transgenerational, young children in the next generation will again become research subjects. According to internationally accepted guidance (*Council of Europe, 1997*; *Doek et al., 2009*; *CIOMS, 2017*), minors may be included in research that has the potential to benefit themselves on the condition that risks are minimized and outweighed by the prospect of individual benefit. If there is no such potential, research with minors is only allowed if (apart from general research ethics requirements) both the following conditions are fulfilled: the research question can only be answered by conducting research with minors (criterion of group-relatedness); and the burdens and risks for those minors are minimal.

For our analysis, this guidance provides important context. Whereas it seems that MAR follow-up meets the criterion of group-relatedness (only research with children can give insight into the possible effect of being conceived through MAR on children's development), procedures involving more than minimal burdens and risks may only be considered when the child themselves can benefit. As indicated earlier, this may be the case when follow-up studies lead to findings revealing health problems or health risks that allow for timely treatment or prevention. An evidence-based likelihood of specific findings in this category would turn MAR follow-up into a form of 'therapeutic research' with minors. If such outcomes are a mere theoretical possibility, however, it would be difficult to take them as grounds for justifying procedures involving more than minimal burdens and risks.

Although more than minimal burdens and risks are acceptable in principle where non-therapeutic follow-up studies are conducted with competent adults able to provide informed consent (see below), adult offspring conceived through MAR are typically included in follow-up only at a stage where the evidence base on the safety of the relevant ART is already quite robust. This means that the potential benefits for children, couples and public health to be expected from such studies will be smaller compared with those of follow-up in the initial stages of the development of a new ART. Moreover, as the ART through which they were conceived may over the years have undergone major adaptations, it will not always be obvious that the results of long-term follow up are still directly relevant for current practice. Therefore, although follow-up with adults allows giving more weight to third-party benefits when balancing these with the burdens and risks of follow-up, the case for doing so tends to weaken with the passing of time.

What we see here is a tension for which there is no easy solution: whereas the need for comprehensive safety data is greatest at the experimental stages of a potentially risky new technology, the scope for generating such data through follow-up studies in children is limited by the requirement of minimal burdens and risks.

RESPECT FOR AUTONOMY

If a follow-up study with either children or adults meets the proportionality requirement, the further criterion of respect for autonomy requires that families and individuals should only be recruited based on adequate informed consent. We summarize what this entails and discuss whether respect for autonomy allows centres or professionals to encourage families of children conceived through MAR to participate in follow-up.

Informed consent for medically assisted reproduction follow-up

As stated by *Faden and Beauchamp (1986)*, for consent to be autonomous, it must be intentional, based on a proper understanding of what is at stake, and also voluntary, in the sense of being made without controlling external influences. As emphasized in this last condition, consent to participate in research should not just be informed, but decisions must be unconstrained and voluntary. Only then can such decisions be autonomous in the sense of being fully owned by those who make them.

The age at which a young person can provide independent consent for participating in research ranges between 16 and 18 years in different jurisdictions. Some countries, i.e. the Netherlands and Norway, maintain a dual consent procedure from the age of 12 years (with informed consent of both the child and their parents needed). Others require the child to be asked to 'assent' to the proposed research on the basis of information adapted to their level of understanding, again with different ages (often around 6–8 years) as from which this would be needed (*European Medicines Agency, 2019*). This notion of 'assent' ('affirmative agreement') has been criticized for being insufficiently clear, and also in its demarcation with the concept of consent (*Baines, 2011*). From an ethical viewpoint, it is important that children who are mature enough to make relevant decisions based on an adequate understanding of the nature of the research and its implications, can do so. Those who are not yet competent in this sense, should not be burdened with choices that are beyond their capacity for autonomous agency (*Hein and Jõesaar, 2015*). For them, the decision about participating in research should be made by their parents. Should a child who is not yet competent consistently resist being subjected to certain research procedures, such resistance should be respected unless participating is clearly in his or her own interest. As we have argued, this is hardly ever the case in the context of MAR follow-up.

Encouraging participation in medically assisted reproduction follow-up

According to a joint expert document from ESHRE and the European Society of Human Genetics 'parents should be encouraged to take part in follow-up studies of health and development of their offspring' (*Soini et al., 2006*). From the perspective of MAR professionals, this claim is understandable: they need the help of these families to be able to fulfill their own responsibility in the matter. But how does such encouragement relate to the requirement that participation should be based on voluntary consent, as stated above? Doesn't encouragement entail a form of mild moral pressure and, if so, would that be morally problematic? We suggest that this depends on whether families of children conceived through MAR (parents and children) can be said to have a certain responsibility to participate in follow-up. To the extent that they do, it can be argued that encouraging them may under certain conditions be acceptable. In the remainder of this section, we discuss two possible grounds for ascribing such a responsibility to the families of children conceived through MAR: parental responsibility and reciprocity.

Parental responsibility

At this point, a distinction must be made between a situation in which a potentially risky new ART is still experimental or innovative, and a situation in which it has become established treatment. In situations of the former kind, parents can be said to have a prima-facie responsibility towards their children to enrol them in follow-up research that may lead to findings revealing possible health problems or health risks that allow for timely treatment or prevention (*Ishii, 2019*). The qualifier *prima facie* refers to the condition that the research in question must be proportional, also taking account of the burdens for the parents and their family. If so, reminding them, if necessary, of this responsibility is not at odds with respecting their autonomy, as long as their freedom to decide otherwise is respected. In cases in which an experimental new ART is introduced in the context of formal research aimed at generating initial data about safety and effectiveness, professionals may even go a step further and present a pre-treatment agreement to participate in follow-up as a condition of access (*Watts et al., 2012*; *Chen et al., 2016*). Clearly this can only pertain to follow-up of incompetent minors rather than to long-term follow-up for which the consent of the then adolescent or adult must be sought. Moreover, a pre-treatment parental agreement to this effect cannot be enforced, given that research participants or their legal representatives can always decide to retreat from a research project in which they participate (*National Academies of Sciences, Engeneering and Medicine, 2016*). Still, obtaining parents' commitment to the implications of the experimental nature of the procedure is important in view of the need to reduce the uncertainties, as soon as possible, about offspring safety that may still exist at this early developmental stage of a potentially risky new ART (*Watts et al., 2012*; *Ishii, 2019*).

As a further condition in this regard, couples undergoing experimental treatment in a formal research setting should be asked to commit themselves to telling their child how they were conceived. A survey-based study exploring the welfare of children born after experimental ooplasmic transfer conducted in the late 1990s showed that almost none of the respondent families had told their children about the mode of conception. The researchers surmise that precisely the use of an experimental procedure may have been an important factor in this decision (*Chen et al., 2016*).

Reciprocity

Clearly, the appeal to 'parental responsibility' loses most of its force when the new ART has become established treatment, meaning that data are sufficient to conclude that there are no serious concerns about its immediate safety (*Provoost et al., 2014*). There may, however, be a further moral reason for participation in MAR follow-up research, including active participation in long-term follow up of those who themselves have been conceived through MAR. The general case for this argument has, somewhat provocatively, been presented by bioethicist John *Harris (2005)*. He argues along two lines. Invoking the rule of rescue, he says that by volunteering as research subjects we can save others from serious harm and that if we can do so without excessive cost to ourselves, we have a duty to respond accordingly. Invoking the principle of fairness, his second argument is that, as members of modern western societies we all considerably benefit from advances in health care, and that, therefore, we have a prima-facie moral duty to reciprocate by contributing to medical research as the social practice that produces those very benefits. Failing to contribute while continuing to profit would amount to a form of morally reprehensible 'free riding' (*Harris, 2005*). According to Harris, the same reasoning extends to parents or other legal representatives deciding on behalf of children or incompetent adults. They may assume 'that the person they are making decisions for is, or would wish to be, a moral person who wants to or is in any event obliged to discharge his or her moral duties'(*Harris, 2005*, p 246).

Harris' argument has met with criticism. Commentators have pointed out that his arguments fail to make the case for the supposed moral duty to participate in medical research (*Brassington, 2007*;

2011; *Shapshay and Pimple, 2007*). With the rule of rescue, the connection between participating in research and possibly saving human lives as a result is far too indirect to generate a similar call of moral duty as in the proverbial pond case where a child is drowning before one's eyes. Moreover, as a candidate research participant, one is hardly ever the only person around who might be able to respond. Also, while it may be true that fairness requires some form of reciprocation, it does not specify content and kind of what this should mean in practice. The most that can be argued is that all of us have an 'imperfect moral duty' to further the general good and that participating in scientific research is just one of many different ways in which we may choose to do so (*Shapshay and Pimple, 2007*). Still, the idea of participating in medical research as a possible way of fulfilling this imperfect duty means that deciding to do so is not entirely supererogatory in the sense of going beyond what morality might require us to consider. If so, it may well make a difference that our discussion is not about medical research in general but about follow-up research, in which only those can be asked to participate who have undergone the very procedure that is now being evaluated in the interest of future patients who may also need it. With regard to a possible contribution to medical research in general, a person need not have any specific reason for choosing this over other contributions that they might make to the general good, things may well be different when considering a request to participate in follow-up research. Here, the fact of being better placed than most others to make this specific contribution to the general good may amount to a moral reason for at least seriously considering such a request.

CONCLUSION AND RECOMMENDATIONS

Adequate follow-up research is an essential condition for introducing and innovating new reproductive techniques in a responsible way. Considering the clear benefits of follow-up for various stakeholders, the reproductive field should put more effort into actively implementing ESHRE's normative framework considering the execution of MAR follow-up. As the relevant studies inevitably involve burdens and risks, it is essential that its proportionality is assessed on a case-by-case basis. Where children who cannot yet themselves consent to participating are concerned, more than minimal burdens and risks are acceptable only where it is reasonable to expect that they themselves can benefit from taking part in the relevant studies. Follow-up research requires the active involvement of MAR families, with parents consenting for their children and adolescents asked to do so for themselves. When seeking their voluntary consent for participating in follow-up that meets the condition of proportionality, professionals may encourage MAR families to partake in follow-up research. The case for this is strongest where a potentially risky experimental ART is concerned, and such encouragement refers to a parental responsibility for the welfare of the child to be. Where such a new ART is introduced in the context of formal research, pre-treatment agreement to participation in follow-up may be presented as a (non-enforceable) condition for access. This also requires a parental commitment to tell their children how they were conceived. Where the relevant ART has become established treatment, there may still be grounds for encouraging parents of children conceived through and the children themselves to partake in follow-up research based on the premise that they are better placed than others to make this specific contribution to the general good.

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