Human Reproduction Open, pp. 1–9, 2020
doi:10.1093/hropen/hoaa003

human reproduction open

OPINION

Between innovation and precaution: how did offspring safety considerations play a role in strategies of introducing new reproductive techniques?

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Submitted on October 31, 2019; resubmitted on December 23, 2019; editorial decision on January 17, 2020

ABSTRACT: The field of reproductive medicine has been criticized for introducing ARTs without systematic research on possible safety risks and for failing to meet the standards of evidence-based innovation held elsewhere in medicine. In this paper, firstly, we ask whether 'responsible innovation' has been a concern for the field, and if so, how it has understood the practical implications of this idea for the development and introduction of potentially risky new ARTs. Secondly, we consider whether the field has indeed fallen short of its responsibilities in this respect, and if so, how things can be improved. To answer these questions, we present three case studies involving the introduction of a new reproductive technology: ICSI, preimplantation genetic testing and mitochondrial replacement therapy. As a framework for analyzing these cases, we used Per Sandin's account of the four dimensions of dealing with risks (threat, uncertainty, action, command) that are central to debates about the possible role of the so-called precautionary principle. We conclude that, although offspring safety concerns have been on the agenda of the debate about bringing the relevant technologies to the clinic, systematic safety and effectiveness studies were not always conducted. As professionals in assisted reproduction have a responsibility to take account of the welfare of the children they are creating, we suggest a policy of proceeding with systematic caution. Legal measures may be needed to ensure that professional guidance is followed in practice. Finally, an open question concerns the threshold for acceptable risk in the context of introducing new ARTs. Multiple stakeholders, including professional societies and patient organizations, should have a role in the urgent debate about this.

Key words: reproductive medicine / responsible innovation / precaution principle / ICSI / preimplantation genetic testing / mitochondrial replacement therapy / ART

Introduction

One concern within the wide range of ethical questions pertaining to developments in reproductive medicine is whether treatment safety is sufficiently taken seriously when introducing new ARTs (Pennings *et al.*, 2007; Van Steirteghem, 2008; Harper *et al.*, 2012; Provoost *et al.*, 2014; Mulder *et al.*, 2018; Sharpe, 2018). Several commentators have pointed out that ARTs have often been, and are still being, introduced without systematic preclinical safety and effectiveness studies and without follow-up of children conceived with those technologies (Dondorp and de Wert, 2011; Harper *et al.*, 2012, 2017; Sharpe, 2018). Although safety and effectiveness are different things, it is important to note that where evidence of effectiveness is lacking, there are no clear benefits that might render possible risks worth taking. In other words, to determine the proportionality of potentially risky new ARTs, data about safety and effectiveness are both needed.

This critique that these data have not systematically been sought invites two different kinds of question. Empirically, the question is whether 'responsible innovation' has been a concern for the field, and if so, how it has understood the practical implications of this idea for the development and introduction of potentially risky new ARTs. Ethically, the question is whether the field has indeed fallen short of its

responsibilities in this respect, and if so, how things can be improved.

In this paper, we aim to answer both questions. In the next three sections, we will first examine how offspring safety considerations did or did not play a role in the history of introducing new ARTs. We do so by presenting three case studies: two from the past, ICSI and preimplantation genetic testing (PGT), and one contemporary, mitochondrial replacement therapy (MRT). Based on the findings, we will then move on to address the ethical question in the Discussion section.

Intracytoplasmic sperm injection

Technique

ICSI is a form of IVF whereby a single sperm cell is directly injected into an egg cell, which makes it possible for men with substantially low sperm quality to have genetically related children. The first human births resulting from ICSI were reported in 1992 (Palermo *et al.*, 1992). Soon thereafter, the majority of IVF centers worldwide adopted the technique (Harper *et al.*, 2012). ICSI can not only be performed with ejaculated sperm (regular ICSI) but also with medically extracted sperm either from the epididymis (micro-epididymal sperm aspiration, MESA) or from the testicles (testicular sperm extraction, TESE).

Offspring safety risks

The most relevant concerns about ICSI were 2-fold. Firstly, it was feared that the mechanical perforation of the egg cell might lead to oocyte injury or lysis (Laufer *et al.*, 1983). Secondly, several authors suggested that the sperm cells used in ICSI could have genetic abnormalities because the technology involves bypassing the mechanism of natural selection. It was thought that this might affect the health of the offspring conceived through this technique (Cummins and Jequier, 1994, 1995). For MESA and TESE specifically, there were also health concerns due to the risk that the sperm cells used might be old or not fully matured (Martin-Deleon *et al.*, 1973; Cummins and Jequier, 1995; Küpker *et al.*, 2002). Older sperm cells show relatively high DNA damage, which might result in embryonic death or, in some cases, offspring abnormalities (Martin-Deleon *et al.*, 1973; Cummins and Jequier, 1994, 1995). The use of not fully matured sperm cells, potentially disrupting the genomic imprinting of the sperm cells, might lead to embryonic death, growth retardation, birth defects and functional disorders (Cummins and Jequier, 1995).

Safety considerations in strategies of introduction

Hardly, any experimental studies were performed prior to the broad introduction of ICSI. Firstly, it was assumed at the time that testing ICSI in animal models was not technically feasible. Secondly, the accidentally discovered technology proved an immediate success in terms of helping couples with male infertility to have genetically related healthy children (Dondorp and de Wert, 2011). As a result, ICSI quickly proliferated in clinical practice with clinics often applying conditions, such as avoiding the selection of immotile sperm, in order to reduce possible risks. MESA and TESE soon became part of clinical practice in most countries as well. An exception to this picture was the decision of Dutch IVF professionals to withdraw MESA and TESE from clinical application in view of the theoretical risks of these forms of ICSI, eventually leading to a national moratorium on MESA and TESE (Dutch Health Council, 1996), that was soon enacted into law. Lifting the moratorium would require animal studies providing a better understanding of the potential risks for the offspring. When reassuring data became available from animal research, sperm cell studies and clinical practice abroad, MESA (2000) and TESE (2007) were again allowed in the Netherlands, but only in a clinical research setting involving data collection and follow-up (Kremer and Visser, 2008). The moratorium was fully lifted only in 2012 (for MESA) and 2014 (for TESE).

Although most commentators stressed the importance of follow-up research as part of the introduction of new ARTs, not many centers actually conducted follow-up of children conceived through ICSI. A notable exception to this was the pioneering center at Brussels Free University Hospital (Bonduelle *et al.*, 1994, 2004, 2005; Leunens *et al.*, 2007; Belva *et al.*, 2011, 2016).

State of the art and current practice

It has since been established that ICSI does not lead to major abnormalities in offspring (Leunens *et al.*, 2007; Pereira and Palermo, 2018). However, male subfertility has been associated with defects in the Y-chromosome. As these chromosomal defects are inherited by male offspring, it has been shown that boys conceived after ICSI more often also have lower sperm quality (Belva *et al.*, 2016). Additionally, ICSI is associated with a significantly increased risk of (very) preterm delivery (Wisborg *et al.*, 2010), lower mean birthweight (Bonduelle *et al.*, 2004) and an increased risk of rare imprinting disorders (Lazaraviciute *et al.*, 2014) in comparison to spontaneous conceived and non-IVF ART pregnancies. Yet, more studies are needed to investigate whether these specific health effects are caused by the technique itself or by other factors, such as underlying paternal conditions (Devroey and Van Steirteghem, 2004; Berntsen *et al.*, 2019). This is especially important in view of the fact that ICSI is increasingly offered for all causes of subfertility (Nyboe Andersen *et al.*, 2008; Boulet *et al.*, 2015; Harris *et al.*, 2016), albeit without data showing it to be more effective than conventional IVF for conditions other than male fertility problems (Van Rumste *et al.*, 2004; Li *et al.*, 2018). In the light of possible differences in the risk profiles of both techniques, this indication creep is another instance of how safety and effectiveness considerations are both relevant for determining the proportionality of assisted reproduction.

Preimplantation genetic testing

Technique

PGT enables the selection of embryos based on an evaluation of their genetic composition. PGT for monogenetic disorders (PGT-M) and PGT for structural rearrangements (PGT-SR) are indication-based applications aimed at helping couples at high risk to prevent transmitting a serious genetic disease to their offspring. These two types (historically referred to as PGD) were introduced in the late 1980s (Handyside *et al.*, 1990). The third type, PGT for aneuploidy (PGT-A) was introduced to screen the chromosomal constitution of IVF-embryos with the aim of increasing the chances of achieving a successful pregnancy. This was historically called PGS and was introduced in 1995 (Verlinsky *et al.*, 1995).

The biopsy needed to perform PGT can take three different forms. Polar body biopsy is rarely used. It only offers information on the maternal contribution to the genome of the embryo. In blastomere biopsy (historically the most frequently used biopsy type), one or two

blastomeres are removed from a cleavage stage embryo at 3 days post-fertilization (approximately 8 cells). In trophectoderm biopsy, several cells are removed from a blastocyst stage embryo at 5 days post-fertilization (150–300 cells).

Offspring safety risks

The main safety concern of PGT is the biopsy needed to collect cells for genetic testing. There are three possible risks associated with PGT biopsies for offspring thus conceived. First, there is the risk of the biopsy procedure itself. The use of a laser, additional actions outside an incubator or specific embryo culture media may have risks for the child conceived after PGT. For example, there is evidence that the use of specific embryo culture media affects important offspring parameters such as birthweight (Zandstra *et al.*, 2015).

Second, the removal of cells may have risks for the development of the embryo. Early studies in mice and humans have shown an association of blastomere biopsy with impaired implantation potential and reduced/delayed fetal development (Tarín *et al.*, 1992; Liu *et al.*, 1993; Tarín and Handyside, 1993). In recent years, the field is shifting to favoring trophectoderm biopsy over blastomere biopsy (Scott *et al.*, 2013; Zacchini *et al.*, 2017). A main reason for this is the increased popularity of PGT-A in many countries, and the aim of overcoming its diagnostic difficulties due to mosaicism when using blastomere biopsy. Trophectoderm biopsy may seem less risky at first glance, as the biopsy does not affect the inner cell mass, of which the cells later form the fetus. In the past, it was thought that 'the loss of a few mural trophectoderm cells should not be important embryologically, since this tissue does not seem to play a fundamental role in the later development of the embryo' (Edwards and Hollands, 1988). More recently, however, it is speculated that removing these cells could result in a smaller placenta, which could lead to incorrect embryo development and abnormalities in offspring (Zacchini *et al.*, 2017; Zhang *et al.*, 2019).

Third, for trophectoderm biopsy, the embryo needs longer *in vitro* culturing than for blastomere biopsy (5 instead of 3 days). The effect of extended embryo culture is still under discussion and thus far little data are available (Youssef *et al.*, 2015). However, as the use of specific embryo culture media affects important offspring parameters such as birthweight (Zandstra *et al.*, 2015), longer embryo culturing may further increase these risks. Additionally, cryopreservation may be necessary more often. Singleton pregnancies following frozen embryo transfer are associated with higher risk of high birthweight babies compared with those from fresh embryo transfer (Maheshwari *et al.*, 2018a), although the interpretation of this finding has led to some debate (Somigliana *et al.*, 2018; Maheshwari *et al.*, 2018b). Yet, data on cryopreservation in combination with PGT-A specifically are still limited (Penzias *et al.*, 2018).

Safety considerations in strategies of introduction

Prior to the introduction of PGT, preclinical research has been performed, particularly in the mouse model (Gardner, 1985; Monk *et al.*, 1987; Wilton *et al.*, 1989). After its introduction, research continued in mice, other animal models and human embryos (Takeuchi *et al.*, 1992; Carson *et al.*, 1993; Pierce *et al.*, 1997). Nevertheless, information on biopsy safety was limited (De Vos and Van Steirteghem, 2001).

Only a few safety measures aimed at decreasing possible offspring safety risks were taken when introducing the new technology. Some centers initially recommended their patients to consider prenatal diagnosis after PGT (Vandervorst *et al.*, 2000). This was, however, mainly to confirm the result of the PGT diagnosis. One understanding at the time was that as biopsy damage would lead to failed implantation, there was no need for much concern regarding surviving embryos (Edwards and Hollands, 1988). Still, regulation involving limiting indications for what was then called PGD to serious conditions was partly also informed by the notion that possible biopsy risks should be proportional to the benefits of selective reproduction made possible by the procedure (De Wert *et al.*, 2014). Similar reasoning may have informed the 2001 decision by the UK Human Fertilization and Embryology Authority (HFEA) not to allow preimplantation tissue typing, stating that there were 'risks arising from embryo biopsy and it was felt that the Ethics Committee had not taken proper account of the absence of evidence of no risk' (House of Commons, 2005). This 'absence of evidence of no risk' has not stood in the way of a rapid global proliferation of PGT-A. Even after its upgrade from PGS1 (blastomere biopsy and FISH) to PGS2 (trophectoderm biopsy and assessment of all chromosomes), evidence for the effectiveness of this procedure is still lacking and the treatment's rationale is under discussion (Scott Jr *et al.*, 2012; Mastenbroek, 2013, 2014; van Loendersloot *et al.*, 2014; Sermon *et al.*, 2016; Penzias *et al.*, 2018; Popovic *et al.*, 2018; Lawrenz *et al.*, 2019). Furthermore, although concerns about the safety of blastomere biopsy (also referring to possible epigenetic effects) are recently stressed by authors with a stake in promoting PGT-A, there seems less interest in how the extended embryo culture needed for trophoblast biopsy may affect the relative risk profiles of both biopsy procedures. Yet, it is well established that culture conditions have an impact on the epigenetics of developing embryos, which may well be more outspoken when the culture period is longer (Zandstra *et al.*, 2015). Only few clinical studies have compared blastomere biopsy with trophectoderm biopsy (McArthur *et al.*, 2008; Adler *et al.*, 2014; Coll *et al.*, 2018).

Only a few centers succeeded in conducting follow-up research on PGT, particularly in combination with blastomere biopsy. One of the leading groups was again the Free University Brussels Hospital (Nekkebroeck *et al.*, 2008; Desmyttere *et al.*, 2009; Liebaers *et al.*, 2009; Beukers *et al.*, 2013; Kuiper *et al.*, 2017).

State of the art and current practice

Follow-up research does not show a higher degree of major abnormalities in children born after PGT in comparison with IVF or ICSI only (Banerjee *et al.*, 2008; Nekkebroeck *et al.*, 2008; Desmyttere *et al.*, 2009; Liebaers *et al.*, 2009; Heijligers *et al.*, 2018, 2019). Although children born following PGT-M and PGT-SR in combination with blastomere biopsy do have an increased risk of adverse obstetric and neonatal outcomes, these seem mainly related to underlying parental conditions, except for an increased risk of placenta previa (Bay *et al.*, 2016). It is important to note that follow-up studies investigating the health of children born after PGT in combination with trophectoderm biopsy are still very limited.

PGT-A was originally recommended and carried out as an add-on to IVF for couples with advanced maternal age, repeated IVF failure, repeated miscarriage and severe male factor infertility. Regardless of the ongoing debate about its effectiveness, the technique is increasingly also offered to younger women with a good pregnancy prognosis (Mastenbroek and Repping, 2014; Penzias *et al.*, 2018).

Mitochondrial replacement therapy

Technique

MRT is a form of IVF in which the future child's mitochondrial DNA (mtDNA) comes from a donor. This technique has been developed to allow women who carry disease-causing variants in their mtDNA to prevent passing these onto their offspring (Hyslop *et al.*, 2016; Greenfield *et al.*, 2017; Zhang *et al.*, 2017). There are several forms of MRT. In maternal spindle transfer (MST), the spindle-chromosome complex is transferred from the prospective mother's oocyte into a donor oocyte from which the same has been removed. The resulting oocyte will then be fertilized *in vitro*. In pronuclear transfer (PNT), the male and female pronuclei are removed from the recipient's fertilized egg prior to their fusing and are inserted into a fertilized donor egg from which the pronuclei are removed (Craven *et al.*, 2010).

Offspring safety risks

Apart from the risk of not preventing transmission of the disease, the main concern with MRT is that manipulation of the (fertilized) egg cell may have adverse effects for the resulting embryo (Adashi and Cohen, 2017). One study showed that 'oocytes that had received their nucleus from a donor were less likely to develop into a blastocyst than oocytes who had had their own nucleus injected back into them' (Hyslop *et al.*, 2016). Yet, it is unclear whether this resulted from suboptimal interaction between the nucleus of the recipient and the mitochondria of the donor, or from the oocyte cryopreservation procedure (Eyre-Walker, 2017; Wei *et al.*, 2019).

Safety considerations in strategies of introduction

In comparison with ICSI and PGT, preclinical research on MRT was more extensive and more structured. The relevant studies were performed in animals (including nonhuman primates) and human embryos (Tachibana *et al.*, 2009, 2013; Craven *et al.*, 2010; Paull *et al.*, 2013). The UK, in particular, has much invested in this research, as it was a precondition for the government to lift legal restrictions and for the HFEA to grant a clinical license. Although many research steps were aimed at improving efficiency, some of them also concerned improving safety, such as studies of epigenetic modifications and gene expression in embryos derived from PNT and MST (HFEA, 2016).

Approaches of introducing MRT vary widely. In 2003, a collaboration between a Chinese group and a team from the USA reported the first PNT (Zhang *et al.*, 2016). The attempt resulted in the death of two fetuses after selective fetal reduction. This ultimately led to the USA and China imposing prohibitive regulatory policies, which still stand today (Ishii, 2018; Ishii and Hibino, 2018). In 2016, US-based scientists succeeded in delivering the first baby as a result of MST (Zhang *et al.*, 2017). The procedure was performed in a clinic in Mexico to avoid the prohibitory policy of the USA. Since then, pregnancies and births using MRT have also been reported in Ukraine for cases of embryo arrest (PNT) and in Greece/Spain to overcome female infertility (MST), again making use of the lack of appropriate regulation (Ishii and Hibino, 2018). In 2015, the UK lifted legal restrictions banning the clinical use of MRT; however, only for licensed clinics under strict conditions, as formulated in scientific reviews conducted by the HFEA. For example, MRT should only be offered to women who have a significant risk of transmitting a serious mitochondrial disease and where PGT is no alternative (HFEA, 2015). Additionally, in order to eliminate the risk of the disease re-emerging in subsequent generations, it is recommended that any female born following MST or PST should be advised to use PGT if she wishes to have children of her own (HFEA, 2013). In 2017, the HFEA awarded a Newcastle group the first UK clinical license, which resulted in their first patient in 2018. This group has accepted various women with different indications, but so far, no pregnancy has been reported. In line with HFEA recommendations, the Newcastle group aims to perform follow-up studies. However, whereas those recommendations insisted on long-term follow-up, for practical reasons, the current aim is limited to gathering follow-up data until the age of 18 months only.

State of the art and current practice

As births following MRT are still very limited and no follow-up data are available, hardly any conclusions can be drawn regarding the effects in children thus conceived. Recently, several fertility centers worldwide have started offering MRT also as a means of 'rejuvenating' the eggs of older women with the promise of increasing their chances of a successful pregnancy, an idea probably inspired by ooplasmic transfer in the 1990s (Cohen *et al.*, 1998). The recently reported life births after MRT in Greece and Ukraine were an instance of this (Devlin, 2019). This premature widening of indications has led ESHRE to issue a strong condemnation, discouraging the use of MRT for fertility problems 'until this technology has been proven to be effective and safe' (ESHRE, 2019). Although MRT for fertility problems may be less risky as carry-over is no issue here, the point remains that, due to a lack of evidence on effectiveness, there are no proven benefits to outbalance the remaining risks.

Discussion

Our case studies provide important context for the increasingly louder claim that, until now, responsible innovation has not been a sufficiently high priority for the field. Where precisely and in what sense might the field have fallen short and, if so, what follows in terms of possible lessons for the future? To answer this, we make use of Per Sandin's four dimensions relevant to dealing with uncertain risks. He presents these in the context of his discussion of the so-called 'precautionary principle'. Following Sandin, the general structure of the precautionary principle can be reproduced as: 'If there is (1) a threat, which is (2) uncertain, then (3) some kind of action (4) is mandatory' (Sandin, 1999). Using these dimensions as a heuristic tool allows us to zoom in on the reasoning behind specific choices made with respect to introducing new ARTs.

It is important to note that using the four dimensions in this way does not in itself entail a commitment to accepting the precautionary principle as a framework for introducing new ARTs. In fact, the so-called innovation principle, where 'the call is for the benefits of innovation to be weighed against known harm' (Read and O'Riordan, 2017), can be understood as dealing with the same issues. The innovation principle provides, however, a different answer at the crucial juncture where the precautionary principle links the uncertainty dimension with a need to take action. By insisting that only 'known' harm can be a ground for limiting the application of new technologies, the innovation principle emphasizes the importance of unhindered innovation, of which the benefits would be frustrated by unnecessary measures of precaution.

As our case studies suggest, it would be difficult to maintain that the field has failed to recognize that new ARTs, involving untested

ways of handling human gametes and embryos, come with possible risks for children thus conceived. In each of the three case studies, there has been quite some discussion of the fact that the then new technology in question (ICSI and its variants, PGT and MRT) might have adverse consequences for the health of the offspring of the applicants. In most cases, concerns about possible offspring risks related to the application of those technologies were hypothetical and had not (yet) been substantiated. Therefore, any account of how risky precisely a new technology was had to include an emphasis on the uncertain nature of the threat, both regarding its chances of materializing and the seriousness of the possible impact this might have on the health of children thus conceived.

There is a range of possible ways of dealing with this uncertainty. On the one end of the spectrum, supporters of the innovation principle may reason that any measures to constrain the introduction of new ARTs or to limit their application for safety reasons should be based on evidence of a significant chance that serious harm could otherwise occur. This view might invite moving new technologies to the clinic without costly and time-consuming preclinical safety studies and refraining from setting safety-related restrictions as long as children are born healthy and no calamities ensue. Some degree of such 'innovation principle-reasoning' may have contributed to the rapid introduction of ICSI in the absence of preclinical safety studies for which a suitable animal model was not available at the time.

On the other end of the spectrum, strong versions of the precautionary principle insist on the opposite: as long as new reproductive technologies pose an uncertain threat to the health of future children, they should not be introduced. Although we did not encounter explicit references to the precautionary principle in our case studies, the Dutch moratorium on clinical applications of MESA and TESE seems a good example of strong precautionary principle-reasoning, and perhaps the same can be said of the US Food and Drug Administration's decision to ban clinical research of MRT pending safety concerns.

If the innovation principle stands for giving innovation a green light in the face of uncertainty, and strong versions of the precautionary principle would stand for giving it a red light, the intermediate, or weaker, forms of the precautionary principle may be understood as inviting an amber light policy, allowing innovation to 'proceed with caution'. What characterizes these as forms of the precautionary principle is their insistence that uncertainty should not be taken as a reason for refraining from safety measures (Sandin, 1999). However, in order to be proportional, these measures do not have to be prohibitive. Using examples from our case studies, relevant measures can, firstly, take the form of research aimed at reducing uncertainty both through preclinical studies using animals and/or human embryos (as in the MRT case) and through systematic long-term follow-up (as done by the pioneering ICSI center in Brussels). Secondly, further measures may include specific restrictions aimed at reducing avoidable risks in the application of the relevant technology. Examples from our case studies include the requirement of using motile sperm for ICSI or setting strict indications for the first clinical applications. A more generally relevant consideration in this respect is that most couples seeking medically assisted reproduction (MAR) are subfertile rather than infertile. This means that in many cases 'tailored expectant management' will help in avoiding unnecessary MAR in those who do not need fertility treatment yet (Eijkemans *et al.*, 2017). Avoiding overtreatment is important not only for economic reasons but also in view of reducing avoidable burdens and risks, including offspring risks (Kersten *et al.*, 2015). Finally, a 'proceed with caution' approach would recommend against piling up procedures with uncertain risks, as in the suggestion at the time of introducing ICSI to use the then still new PGT technology for checking the genetic health of ICSI-embryos (Morris and Gleicher, 1996).

In each of our case studies, we found instances of expanding the use of a potentially risky technology to applications for which its effectiveness has not been proven. This applies to the increasing tendency of offering ICSI for non-male fertility problems, to the widespread use of PGT-A as a general add-on to IVF and to recent reports about MRT being offered for oocyte rejuvenation and embryonic arrest. Instead of taking safety as an absolute criterion, assessing whether a technique is safe enough is rather a matter of proportionality. By using a potentially risky technique for indications that lack evidence of effectiveness, those risks do not weigh up against the benefits. While it may be an open question whether the innovation principle could be invoked for justifying these practices (does the principle allow ignoring uncertain risks also if there are no proven benefits that might be frustrated by restrictive measures?), it is clear that these unproven expansions are squarely at odds with even the weakest versions of the precautionary principle.

Although our case study analysis suggests that it would be wrong to conclude that responsible innovation has not been a concern of the field, it is also clear that this has not been a systematic and shared endeavor of the field as a whole. Relevant ESHRE guidance (Pennings *et al.*, 2007; Provoost *et al.*, 2014) seems to be taken by fertility centers as expressing non-committal suggestions rather than stating shared professional responsibilities. Clearly, this should not be a problem if the innovation principle is to determine what counts as responsible innovation. While that may sound quite attractive in a field that to a large extent is driven by commercial interests, it is not a tenable position from an ethical point of view. As acknowledged by ESHRE, professionals working in human reproduction inevitably assume a responsibility to take account of the welfare of the children they are causally involved in creating (Pennings *et al.*, 2007). As it seems that what we have referred to as weaker forms of precautionary principle are best able to capture this double responsibility, it is crucial that the corresponding approach to responsible innovation should not remain a pious wish. In terms of what Sandin refers to as the 'command dimension' of dealing with uncertain risks, our case studies suggest that without the backing of legal frameworks (such as those governing the introduction of MRT in the UK), current professional guidance lacks sufficient commanding power to ensure that new technologies are not introduced without research efforts aimed at reducing uncertainty about the nature and magnitude of offspring risks.

Inevitably, this leads to the question of what the threshold for acceptable risk should be. Clearly, the view that MAR is only acceptable if it leads to perfectly healthy children lays the bar too high. Not only does all reproduction come with risks, the trade-offs relevant to MAR are different from those in natural reproduction. However, the fact that some patients are desperate enough to accept even high risks for the child-to-be rather than remain childless does not mean that it should be left to individual patients or couples to determine what risks are still acceptable. As elsewhere in medicine—and even more so in MAR-given professional co-responsibility for the welfare of the child—informed consent is a necessary, but not a sufficient, condition for what might count as responsible treatment (Dondorp and De Wert, 2011).

According to ESHRE's Task Force on Ethics and Law, the bottom line is that assisted reproduction should not entail a high risk that the child would have a seriously diminished quality of life (Pennings *et al.*, 2007). Still, more debate seems needed on the most appropriate criterion for acceptable risk in the context of introducing new ARTs.

Conclusion and recommendations

In each of our case studies, offspring safety concerns have been on the agenda of the debate about bringing the relevant technologies to the clinic. However, apart from settings where this was legally required, systematic safety and effectiveness studies (in line with ESHRE guidance) were not always conducted. One possible reason for this is the different views about how to deal with the uncertain (often theoretical) nature of the risk. As we have argued, an innovation principle approach seems at odds with the notion that professionals in assisted reproduction have a responsibility to take account of the welfare of the children they are creating. While strong (prohibitive) forms of the precautionary principle seem difficult to justify in the light of the equally morally important interests of those dependent on medical help for having children, we suggest a policy of proceeding with systematic caution.

Although follow-up research has shown that up until now, only few adverse health effects of new ARTs have emerged, this should not be taken as a reason for complacency. As new reproductive technologies are on the horizon that appear to come with potentially significant offspring risks (including the reproductive use of stem cell-derived gametes or genetically modified embryos), this should be regarded as a matter of concern that may require both professional societies and governments to take a more active role in safeguarding the responsible development of these technologies. Although this should be primarily a matter of self-regulation, governments can play an important role in terms of providing a legal context for such self-regulation and for ensuring compliance with its provisions.

Finally, more debate seems needed on determining the threshold for acceptable risk in the context of introducing new ARTs. Multiple stakeholders, including professional societies and patient organizations, should have a role in this.

Authors' roles

All authors contributed to the conception and design of this paper. The first author has drafted the article and all authors contributed in revising it critically for important intellectual content. Finally, all authors have approved this version of the paper.

Funding

This project is financed by the Funding Agency for Innovation by Science and Technology in Flanders (IWT), project number 150042 (Science and Ethics of stem cell derived Gametes; SEGa).

Conflict of interest

The authors declare that they have no conflict of interest.

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