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Innovative reproductive technologies: risks and responsibilities

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ABSTRACT: In view of the global burden of subfertility, efforts are required to make assisted reproduction more effective, less burdensome and more equally accessible. New reproductive technologies are frequently introduced in clinical practice without a sound evaluation of their efficacy, effectiveness and/or safety. Safety issues in this context refer both to patients (mostly women) undergoing the relevant medical procedures, and to the health of children born as a result. Responsible innovation requires making potentially risky reproductive technologies the subject of research, ideally proceeding through the steps of preclinical investigations, clinical trials and (long-term) follow-up studies. The European Society of Human Reproduction and Embryology is especially equipped to take the lead here.

Key words: assisted reproduction / IVF/ICSI outcome, ethics / innovation / safety

Introduction

More than 4 million children have been born after IVF, mostly to parents who would otherwise not have been able to enjoy this fulfilment of a deeply held human desire. This would not have been possible but for the fruits of constant innovation within the highly dynamic field of medically assisted reproduction. Contrary to the impression that may arise from media hype and ensuing debates, assisted reproduction is fundamentally a morally sound, not a morally problematic practice.

This also means that there is a moral imperative for further innovation: to make assisted reproduction more effective, less burdensome for the women involved and more widely accessible to those who without this technology would not be able to have children or those who, because of a high risk of having a child affected with a genetic disease, would otherwise not be able to reproduce with confidence.

Innovative treatment or research?

There are two forms of innovation in medicine (Eaton and Kennedy, 2007): formal 'medical research' on the one hand and 'innovative treatment' or 'clinical innovation' on the other. The latter is what clinicians do when they try something new that has not yet been thoroughly tested in a research setting. For instance a new surgical technique or the off-label use of certain drugs. This form of innovation circumvents the strict requirements and rules of formal research (Margo, 2001). As a result, patients may not always be aware of the experimental nature of proposed innovative treatment, nor about

possible risks. Furthermore, although innovative treatments often lead to publications, these are mostly not of the kind that will yield robust data about the efficacy and safety of the relevant procedures. They often refer to series of patients that are compared with historical cohorts using a diversity of clinical outcome measures rather than being formally structured to include blinding, randomization and clear prospectively designed endpoints. As a consequence, insufficiently validated treatments may find their way to regular practice.

The positive side of having this option of innovative treatment, some will argue, is that it allows innovations to become available for helping patients sooner than would have been possible if the lengthy and arduous route of regulated research were chosen. A good illustration is the off-label use of anti-retroviral and anti-infective drugs that turned out to be life-saving for thousands of patients who otherwise would have died of AIDS (Wilkes and Johns, 2008). In the light of such examples, there is an understandable feeling among many practitioners that the research route stifles innovation. On the other hand, illustrations can also be given of cases where procedures were introduced into clinical care without proper testing that later on turned out to be ineffective or harmful. In the context of medically assisted reproduction the premature introduction of preimplantation genetic screening (PGS) for aneuploidy is a good example. This was introduced as regular care in many clinics, but in subsequent trials turned out not to do what it was thought to do, with the possible implication of reducing rather than enhancing chances of successful pregnancy (Geraedts and De Wert, 2009). On the initiative of the Pre-implantation Genetic Diagnosis (PGD) Consortium of the European Society of Human Reproduction and Embryology (ESHRE), PGS is now in the process of being re-evaluated in a different form

(polar body biopsy and analysis of all chromosomes) in a proper research setting (Geraedts *et al.*, 2010; Harper *et al.*, 2010).

According to authoritative documents, including the Helsinki declaration (World Medical Association, 2008) and the American Belmont report (National Commission, 1979), innovative treatment ought to be made the object of research as soon as this is practically possible. An obvious problem is the difficulty of distinguishing between innovative treatment and mere adaptations of clinical management (Reitsma and Moreno, 2005). In cases such as the use of new instruments, or a slightly different surgical technique, it would be absurd and impossible to require that everything new should be introduced through the route of research. This is why the Belmont report uses the qualifiers 'radically new procedures' and 'major innovations'. Clearly, the distinction between what is and is not radically new, and between major and minor will remain a matter of opinion. What about changes in culture media used in IVF laboratories? Most practitioners would seem to feel that these are adaptive practices rather than major innovations. This may depend on the nature of the substances used and what is already known about their features and safety profile from use in other contexts.

However, let us focus on what are clearly major innovations in the field of medically assisted reproduction. The historical record shows that several such innovations have been introduced in clinical practice without much preclinical research into their effectiveness and safety. One may think here of cryopreservation of embryos, ICSI, ooplasm transfer and most recently oocyte vitrification. Is there a problem with this? Has not the history of IVF and related technologies been a continuing success story, leading to reassuringly healthy children in the vast majority of cases? No serious safety problems have emerged, apart from the adverse health effects of multiple pregnancies (especially higher order multiples), something that the field is now trying to prevent. However, recent reviews have suggested that singleton IVF-children are also at a higher risk of adverse pregnancy outcomes including preterm delivery and a low-birthweight (Halliday, 2007; McDonald *et al.*, 2009). The cause of this is unknown and may be related to one or more of the various technical variables of IVF, or to factors related to subfertility *per se*, or to both. A specific cause for concern is that certain rare imprinting disorders such as Beckwith–Wiedemann Syndrome have been found to be significantly increased after IVF (Amor and Halliday, 2008; Owen and Segars, 2009). Furthermore, epigenetic modifications may perhaps put IVF children at a higher risk not only of pregnancy complications and specific birth defects, but also of more subtle effects on their long-term health, including an increased susceptibility for developing cancer and other common diseases (Niemitz and Feinberg, 2004; Katari *et al.*, 2009). The precise implications of this are still unclear. Some commentators have suggested that we may be looking at the tip of an 'epigenetic iceberg' or sitting on a ticking 'developmental time bomb' (Maher *et al.*, 2003; Grace and Sinclair, 2009). Others will find those images far too dramatic and unnecessarily alarming.

The case for responsible innovation

Whoever is right here, these concerns remind us of the special nature of IVF: a procedure with consequences not just for those wanting to

be treated. Of course, the first responsibility of fertility professionals is towards their patients. But as stated by ESHRE's Task Force Ethics & Law, the causal contribution of fertility professionals to the establishment of pregnancy makes them co-responsible for the welfare of children born as a result (Pennings *et al.*, 2007). Moreover, given the interest of society in the good health of future generations, possible public health effects should also be taken into account (Young, 2001; Sinclair *et al.*, 2007). If a possible link between IVF and epigenetic modification leads to a small increase in the relative risk for cancer or other common diseases, the public health impact may be considerable. The field is already taking this perspective with regard to advising patients about preconceptional life style issues (Dondorp *et al.*, 2010). But if we are concerned about the lower birthweight of children of women who continue to smoke during pregnancy, then certainly we should also be concerned about the lower birthweight found in IVF singletons.

In the light of these interests and responsibilities, a strong case can be made for a more ambitious approach to innovation in medically assisted reproduction than the field has generally shown in the past. We need to know more about the health impact of new reproductive technologies for all interested parties (women, children, society) before accepting them as part of the standard toolbox.

Animal research

Ideally, innovation should start with preclinical research in animal models designed not only to test feasibility, but also to investigate the safety of a new technology (Pennings *et al.*, 2007). Obviously, much experience has been gathered from the use of reproductive technologies in farm animals, showing that these technologies may contribute to differential pregnancy outcomes (Loneragan, 2007; Sinclair, 2008).

Where possible and useful, animal safety studies are crucial in that they allow the study of multigenerational effects in a shorter time span. No such studies were done prior to the introduction of ICSI, not only because testing in animal models was too readily assumed to be technically impossible, but also because of the immediate success of the new approach, leading to the birth of healthy children (Te Velde *et al.*, 1998; Hewitson, 2004). In the case of oocyte freezing, systematic preclinical studies in animals were undertaken, but only after early clinical applications led to high failure rates caused by chromosomal damage (Oktay *et al.*, 1998).

A case can be made for considering the possibility of safety studies in primate models as these are more close to humans (Bavister, 2004; Hewitson, 2004). In a recent interview John Biggers recounts an early debate at an NIH meeting about the possible funding of clinical IVF research in the USA (Biggers and Racowsky, 2008; Biggers, 2010). At this meeting in the late 70s, the notion was discussed that women should not be exposed to IVF treatment until the safety of the methods had been worked out using monkeys. Although this proposal was supported by some of his most influential colleagues, Biggers felt it would take too long and be too expensive. 'I felt that we already had enough information to proceed with caution. The committee accepted my point of view' (Biggers and Racowsky, 2008). An opposing view, stressing the need for prior animal research, was one of the reasons why the British Medical Research Council (MRC) had rejected the application of Edwards and Steptoe a few years earlier (Johnson

et al., 2010). As a consequence of that decision the work leading to the birth of Louise Brown proceeded with funding from private donors and in the form of innovative treatment rather than through the formal research approach that the rejected application had aimed at. Looking back at these debates and given the uncertainties that the field still faces over long-term safety effects, one may ask whether a useful third option might have been a multi-track approach in which parallel to 'proceeding with caution', safety studies in monkeys were also conducted. As the life span of appropriate primate models (old world monkeys) is considerable shorter than that of humans, it is conceivable that this would by now have begun to yield some of the insights we currently expect from long-term, ideally also multigenerational follow-up in children born after IVF. Of course the costs of such research are huge, and primate research is an even more sensitive issue in society than animal research using mice and rats. But whenever a case can be made for the usefulness of such parallel long-term safety studies in primates, these considerations need not be categorically prohibiting.

Embryo research

Even when preceded by reassuring animal studies, the step to first clinical experiments inevitably involves a leap of faith. Indeed, the question is how much animal research is enough and when it is safe to move on to human application. In this connection, research using human preimplantation embryos may be an important intermediate step (Pennings *et al.*, 2007). Quite some time ago several commentators referred to cryopreservation and *in vitro* maturation of oocytes as examples of new technologies where preclinical embryo research might be useful (Health Council of the Netherlands, 1998; De Rycke *et al.*, 2002). This would involve creating embryos from oocytes having undergone the relevant manipulations and using the resulting embryos for (additional) safety studies, focusing on possible effects on developmental processes and epigenetic mechanisms. Underlining the importance of this type of research, Anne McLaren once compared the direct clinical introduction of innovative technologies in assisted reproduction with 'making the first test of a new aircraft-guidance system on a crowded Boeing 747' (McLaren, 1989).

As this sounds quite sensible, why is it that in cases where preclinical embryo research might have been possible, this step is usually skipped? Part of the explanation is probably that many centres do not like the idea of further delaying the introduction of a new technology that they find promising and feel confident about, especially if there is competition between groups. But legislative limits also play a role. The categorical prohibition of creating embryos for purposes of research in the European Convention on Human Rights and Biomedicine and in the law of many European countries means that even if centres want to conduct the relevant type of safety studies in embryos, they are legally not allowed to do so. It is ironic that society gives so much protection to the human embryo that as a consequence women and children are put at greater risk (Health Council of the Netherlands, 1998). The reasoning behind the prohibition is difficult to sustain given the broad consensus about the relatively low moral status of the preimplantation embryo presupposed in the justification of IVF itself (Devolder, 2005; Dondorp and De Wert, 2007). Indeed, the question is not whether human embryos may be created for instrumental purposes, but what purposes are important enough

to justify doing so and under what further conditions. Clearly, research involving the creation of human embryos can only be acceptable if the necessary donor-oocytes are obtained in a morally responsible way, including stimulation protocols that minimize the risks for the women involved (De Wert and Mummery, 2003).

The adverse effect that embryo protection legislation may have on the scope for responsible innovation has become clear in the case of Italy. Here the intention of the Legislature has been to rule out the instrumental use of human embryos in the context of IVF. In order to avoid embryos becoming surplus, the Italian law of 2004 obliged practitioners to transfer all embryos to the womb in the same cycle in which they were created (Boggio and Corbellini, 2009). One effect of this ruling was the turn towards cryopreservation of surplus oocytes through slow freezing and vitrification (Ubaldi *et al.*, 2010). This has given a strong impetus to the further development of these techniques and some Italian clinicians argue that IVF-practice in their country has improved as a result. But the point here is that legislation taking the supposedly moral high ground of absolute embryo protection may in fact be morally problematic if it leads to new techniques being prematurely introduced into clinical practice. Responsible innovation is not just a responsibility of clinicians, but requires that legislators and policy-makers take their share as well (Dondorp and De Wert, 2007).

It seems that by now the rapid dissemination of oocyte vitrification has rendered the idea of preclinical embryo research a superseded proposition. But here again a case can perhaps be made for a parallel or multi-track approach. Accepting clinical introduction as a fact need not mean that there can be no further role for trying to learn more about the safety of the procedure by doing research in human embryos. Embryo research can possibly also be useful as part of an effort to find out if certain elements of current IVF-treatment may perhaps contribute to the findings about a higher risk of adverse perinatal outcomes in singletons.

Clinical studies

When, ideally after sufficiently reassuring animal and embryo studies, new technologies are introduced into clinical practice, it is of utmost importance that this is done in a way aimed at prospectively collecting uniform data about effectiveness and safety. The pioneering Brussels centre has made a laudable and important contribution to this with regard to ICSI, and some other centres worldwide have done the same. But it would have helped in generating the large database that is needed if all centres starting with ICSI had taken their share in this. There is a tendency that centres simply copy successful innovations without assuming the responsibility to also do their part in the research aimed at evaluating clinical outcomes.

Large multicenter prospective follow-up studies are needed in order to evaluate not just short-term, but also medium- and long-term outcomes of several forms of assisted reproduction, stretching into and beyond reproductive maturity. Protocols for these studies should be carefully and uniformly designed in order to allow them also to pick up more subtle health effects. Whatever the reasons and possible justifications for taking shortcuts when it comes to doing preclinical safety research, there can be no excuse for not trying to find out about the effects of new forms of treatment, also in the long run. The recent debate about possible epigenetic effects

that may be associated with diseases later in life should give the field as a whole a strong motive for coordinated efforts to ensure that long-term follow-up studies are a central part of its innovation strategy for the future. This of course presupposes the active participation of IVF families and requires the continuing consent first of the parents but then also of the maturing child as it grows into adulthood.

Implementation

It is one thing to refer to an ideal model for responsible innovation, it is quite another to implement this in practice. Although it is clear that individual practitioners share in the responsibility of the field to get this off the ground, their powers are limited. They are subject to the rat race between innovating centres that leaves little room to take time for additional research. And if they themselves would prefer to take a more cautious route to innovation, it may be difficult to find funding for anything beyond feasibility studies. They may also be under strong pressure from patients to go ahead with innovations if expected benefits were already set out in the press. An imaginable response is to try to shift all responsibility to the patients under the heading of 'informed consent'. If patients agree to be treated with an innovative technique, being warned that not much is yet known about possible adverse effects, then what is the problem? The problem is of course that clinicians remain responsible for what they do, not just with regard to consenting patients but also in view of the welfare of any children that will be born as a result and with regard to the interests of society at large.

A role for ESHRE?

To a large extent, responsible innovation will remain a pious ideal if this is not actively supported by professional societies and regulators where they exist. The importance of this is clear if we do not just look at examples of innovation in the past, but also at future innovations that can already be expected. Nuclear transfer aimed to avoid the transmission of mitochondrial disease is one example (Tachibana *et al.*, 2009). The use of artificial gametes (created from human embryonic or induced pluripotent stem cells), at first for basic research and in the context of stem cell therapy, but eventually perhaps also for reproduction, is another (Marques-Mari *et al.*, 2009). Responsibly introducing these new technologies will be a great challenge that the field cannot just leave to individual centres and practitioners (Mertes and Pennings, 2009).

We think that ESHRE is especially equipped to take the lead here. Doing so fits in with its existing commitment to responsible innovation, as shown for instance in the case of PGS (Harper *et al.*, 2010). We are not proposing anything entirely new, however, we think that this existing commitment can be strengthened by concrete initiatives on several fronts.

First, building on elements already in place (like Task Force documents), it is important to further develop an explicit framework for responsible innovation. This would serve not only as a point of reference for the field itself, but also demonstrate its commitment to being accountable to patients and to society at large (O'Neill, 2002; Franklin and Roberts, 2006).

Secondly, this framework needs to be filled in and adapted to tangible fields of innovation. Thinking of the envisaged framework as

something that would engage different layers of the ESHRE community, we see an important role here for the expertise accumulated in ESHRE's Special Interest Groups (SIGs), including the SIG for Safety and Quality in Medically Assisted Reproduction. This should lead to more concrete guidance with regard to issues such as when preclinical studies are needed and of what sort, the level of (un)certainly at which the step to first applications in humans can be justified and on the basis of what criteria, whether parallel animal or embryo studies may still be useful after clinical introduction, how much evidence about effectiveness and safety there must be before the label of 'experimental' can be lifted, and how long-term follow-up studies can be optimally designed to yield useful information.

Thirdly, the problem that really important research is often impossible because of lack of funds, leads to the question whether ESHRE can do more to help overcoming this problem, either by direct (co-)funding or through indirect ways of organising funding. Since an increasingly important motive for evaluating assisted reproduction is its public health impact, other societal actors: governments, public health agencies, pharmaceutical industries and health insurance companies can be asked to contribute to this as well. Patient organizations can play a role in discussing the importance of participating in follow-up research. Getting the required research off the ground should be a joint responsibility of the field and of society as a whole.

Finally, ESHRE might use its influence to call upon society to take its responsibility also with regard to proper regulation. One important concern is that strict privacy regulations may hamper research using health registries. Society should also be asked to refrain from or lift laws and regulations that may sound impressive in terms of embryo protection but that have the perverse effect of limiting the options for preclinical safety research. Categorical bans are often a doubtful sign of moral one-dimensionality. On this point the European Convention for Human Rights and Biomedicine needs to be changed.

Concluding remarks

We have called for a continuous and explicit commitment from the field to the ideal of responsible innovation. An important further question that we have not addressed but want to put on the agenda is how to respond if IVF or specific applications (or their use in specific populations) turn out to lead to subtle adverse health effects such as a somewhat higher risk for cancer or other adult diseases. Some may think that assisted reproduction is only acceptable as long as it leads to perfectly healthy children. In our view, this is untenable. IVF, or some variant thereof, that leads to a happy child with a somewhat higher chance of disease later in life may still be responsible treatment. But inevitably, the question becomes what technology-related risks are still acceptable, both in the light of the welfare of the future child and from a public health perspective. Addressing such questions in a way that confirms the commitment of the field to responsible innovation is a requirement of accountability and a condition for trust.

Authors' roles

Both authors have significantly contributed to the conception and the drafting of this paper; the paper was presented by the first author as a key-note lecture at ESHRE's annual congress in Rome on 28 June 2010.

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