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Evidence for Nuffield Council

Mitochondrial Donation: ethical issues.

This evidence places the proposed treatment in the context of assisted conception treatment (ART) within which it would be provided. It describes situations over the past 20 years where similar ethical dilemmas in the ART have been addressed. In doing so it does not underestimate or refute the current issues but provides prior examples of how they have previously been addressed and the consequences.

1. Understanding human fecundity.

1.1. Every parent wishes to have a child that is healthy. Sadly human reproduction is far from perfect. About 2% of all children born have a congenital abnormality[1] . Thus the outcome of any proposed new treatment must be measured against this standard not ideal aspiration. The risk that a child has a congenital abnormality after being conceived by IVF or ICSI is about 4%.[2] It is thought that this increase over normal conception does not relate to the technical procedures of IVF/ICSI but to the fertility potential of those who need treatment (i.e. they include those who may be considered to have compromised reproductive potential).[3] [3]

1.1 It is appropriate that all steps possible must be taken to make sure that new techniques are evaluated as far as possible. Nonetheless, any assessment of risk for the child must be balanced against the background risks in human reproduction. If it is not possible to give parents a guarantee of a healthy human baby with natural conception then is it unrealistic to expect a new procedure to have better outcomes.

1.2 This may also be relevant to a future situation that might arise. If we are extremely unlucky and the first child born has an abnormality that is considered to be incidental, how do we manage requests for further treatment e.g. how many abnormalities need to be seen before the program is stopped?

[1] http://www.binocar.org/content/Annual%20report%202009.pdf
[2] Maryse Bonduelle , Inge Liebaers1, Veerle Deketelaere, Marie-Paule Derde M Camus, Paul Devroey and André Van Steirteghem 2002. Neonatal data on a cohort of 2889 infants born after ICSI (1991–1999) and of 2995 infants born after IVF (1983–1999) Hum. Reprod. 17 (3): 671-694.
[3] William M. Buckett, Seang Lin Tan, 2005,Congenital abnormalities in children born after assisted reproductive techniques: how much is associated with the presence of infertility and how much with its treatment? Fertility and Sterility 84, 5 ,1318-1319

2 Comparison with PGD.

2.1 A similar analogy to the current debate was the introduction of PGD in the UK. The contemporary, successful introduction of PGD was a major factor in the success of the Parliamentary debate that resulted in the HFEAct in 1990. This technique requires a potentially catastrophic manipulation to the early cleaving embryo. There was little knowledge at that time of pre-implantation development and thus there was little that could be done to assess the risk before implementing a clinical procedure apart from ongoing development of the embryo after biopsy. Similar to those with mitochondrial mutations, couples requesting PGD carried a significant risk that they would have a child naturally that would have a serious disease. PGD was an unknown option with clear theoretical benefit. Thus the PGD was accepted despite the unknown risks because it offered a better chance for the child than that which existed by natural conception. This analogy does not dismiss the current debate but indicates that there have been precedents and some of the debates at that time are pertinent. There was extensive debate that included PGD in Parliament before the HFEAct and the debate is ongoing.[4]

2.2 European data on PDG outcomes is recorded voluntarily.[5] The live birth rates after PGD now are about 16%. The misdiagnosis incidence was 4/1437 babies but there is no evidence that the children born after this technique are at any increased risk because of the pre-implantation procedure. The rate of congenital abnormalities (unrelated to the inheritable genetic problem) is 4% which is similar to that found after ICSI. The first PGD was carried out in 1989 and at this time there is no information about the outcomes for the next generation although it is not anticipated that there will be any problem.

3 Comparison with ICSI (Intracytoplasmic sperm injection)
3.1 ICSI involved the injection of a whole live sperm directly into the egg to achieve fertilisation. This is highly unphysiological as in normal conception only a small part of the sperm enters the egg.

3.2 When ICSI was first started in the early 1990s, there was no prior information about the outcome for the children. There was at that time considerable discussion about the risk. Indeed this resulted in a delay by the regulators that resulted in a

[4] Introduction: Introducing Innovation into Practice: Technical and Ethical Analyses of PGD and ICSI Technologies [article] Journal of Law, Medicine and Ethics, Vol. 26, Issue 1 (Spring 1998), pp. 5-6 White, Gladys B. ; McClure, Michael E. 26 J.L. Med. & Ethics 5 (1998)
[5] V. Goossens,G. Harton, C. Moutou, J. Traeger-Synodinos, M. Van Rij and
J.C. Harper ESHRE PGD Consortium data collection IX: cycles from January to December 2006 with pregnancy follow-up to October 2007Human Reproduction 24;8,1786-1810

later implementation of ICSI in the UK compared with other European countries. It was however the only treatment option for couples where there was a severe male factor problem. In the UK now >5000 babies are born as a result of ICSI treatment each year.[6] There was theoretical concern for these children that was again not dissimilar to the earlier debate about PGD and the current debate about the MST/PN.[7] Extensive follow up worldwide has not revealed any significant problems for these children.[8] Arguably, if it had been introduced in the current UK regulatory climate, it is possible that we would have needed to wait until birth outcomes were well established from studies in other countries before it was introduced.

3.3 There have been other developments in IVF over the past 30 years that have also been associated with risk and similar concerns. These include cryopreservation of embryos,[9] egg donation, post-menopausal conception, the use of testicular sperm and new culture media. Current debates relate to extended culture and potential epigenetic modifications[10][11] and in vitro maturation of eggs.[12] Thus those in the IVF field are not dismissive or unconcerned about the potential risks involved in MST/PN but we approach the issue on the basis of prior experience.

4 Concern for the grandchildren.

4.1 The potential risk for the next generation has also been considered in relation to ICSI. [13][14] It is known that a small number of men who have severe sperm

[6] http://www.hfea.gov.uk/docs/Latest_long_term_data_analysis_report_91-06.pdf(1).pdf
[7] Guido M.W.R. de Wert1 1998 Ethics of intracytoplasmic sperm injection: proceed with care. Human Reproduction 13;1, 219-227.
[8] A. Ericson B. Källén Congenital malformations in infants born after IVF: a population-based study. Hum. Reprod. (2001) 16 (3): 504-509
[9] Cryopreservation of embryos and oocytes: obstetric outcome and health in children. U.-B. Wennerholm Hum. Reprod. (2000) 15 (suppl 5): 18-25
[10] Seamark and Robinson. 1995 Potential health hazards of assisted human reproduction: Potential health problems stemming from assisted reproduction programmes. *Hum. Reprod.* 10 (6): 1321-1322.
[11] Jeremy G. Thompson1, Karen L. Kind, Claire T. Roberts, Sarah A. Robertson and Jeffrey S. Robinson Hum. Reprod. (2002) 17 (11): 2783-2786.
[12] Gary N. Piquette, 2006 The in vitro maturation (IVM) of human oocytes for in vitro fertilization (IVF): is it time yet to switch to IVM-IVF? Fertility and Sterility 85:4,833-835.
[13] Assisted reproductive technology may increase clinical mutation detection in male offspring Chun Feng, M.D.Li-Quan Wang, M.D., Ph.D.Min-Yue Dong, M.D., Ph.D.He-Feng Huang, M.D. Fertility and Sterility 90, 1 , 92-96
[14] Intracytoplasmic Sperm Injection Survey of World Results 2000 B. Tarlatzis, H Bili Annals of the New York Academy of Sciences 900;336–344, April 2000

problems will have abnormalities in their Y chromosome. They will pass this on to their male children. Although this is not a life threatening problem, it would be likely to cause similar subfertility and the associated distress. This is an issue that is routinely discussed with couples before embarking on ICSI treatment. Experience indicates that it is exceptional that couples decline treatment on the basis of this information. Nonetheless this remains a choice that the couple make. It has never been suggested that sex selection should be carried out in these circumstances in favour of females. I am not aware of whether the HFEA has ever been asked to consider such a case or whether or not they would agree to a licence - but the question could be asked.

5 Do abnormal embryos make babies?

If an embryo is transferred to the uterus at the earliest stages of development it has to have the full potential for implantation and development. We know from the examination of IVF embryos that are not transferred, that at least 25% will be genetically abnormal and this is higher in older women.[15] This is despite the fact that many will be morphologically of good quality. Thus it must be assumed that we frequently transfer genetically abnormal embryos into the uterus during routine IVF treatment. Despite this most babies are born without genetic abnormalities. It has been accepted for many years that the process of early development in the uterus must be selecting those with potential for normal growth.[16] There is no reason to expect that babies conceived after manipulation of the oocyte or zygote would not be subject to the same developmental selection. If preclinical data shows that the outcome at the preimplantation stage (that is currently being investigated) is similar to that of routine IVF, even if it shows abnormalities, then this should give some reassurance that clinical trials should be permitted. A concern might be the theoretical possibility that the manipulation of the oocyte or zygote gives rise to an abnormality that is not detected by the current selection processes. Taking a more distant perspective is reassuring. The integrity of reproduction of a species genome is highly conserved in evolution and there is no reason to think that PN/ST would make an exception. The success of the techniques in other species is

[15] A high degree of aneuploidy in frozen-thawed human preimplantation embryos
E. Iwarsson, Monalill Lundqvist, José Inzunza, Lars Ährlund-Richter, Peter Sjöblom, Örjan Lundkvist, Niklas Simberg, Magnus Nordenskjöld and Elisabeth Blennow
1999 Human Genetics 104, 5, 376-382,

[16] Michelle Plachot, Anna Veiga, J. Montagut, J. de Grouchy, Gloria Calderon, Sabine Lepretre, Anne-Marie Junca, J. Santalo, Elisabeth Carles, Jacqueline Mandelbaum, P. Barri, J. Degoy, J. Cohen, J. Egozcue, J.C. Sabatier and J. Salat-Baroux 1988 Are clinical and biological IVF parameters correlated with chromosomal disorders in early Life: a multicentric study Hum. Reprod. (1988) 3 (5): 627-635.

reassuring although not conclusive. Since we don't know what is unknown, the possibility of adverse outcome will always be present but unquantifiable (but great for science fiction).

6 Parental choice.

6.1 All couples take the 2-3% risk that they will have a child with a congenital abnormality when they conceive. The State does not have any role in evaluating this risk on behalf on the child or preventing conception; conversely the right to have a family is enshrined in legislation.

6.2 The question needs to be asked 'who takes the risk' in relation to ST/PN and 'who lives with the consequences'. In clinical practice it is always said to be the patient, based on the giving of informed consent. When treatment involves the creation of a new child for the couple, the parents take on that risk as well. The professionals providing treatment (both clinical and scientific in this case) carry the potential risk that they have provided new treatments that might have bad outcomes. Thus it is the patients, and to a lesser extent the clinicians, who take the risk and will have to live with the consequences. In reality, this situation brings other players who take little risk and minimal consequences. This includes politicians (who make the law), regulators (who will provide the licence) and their advisors (upon those advice they will make decisions), the opposition groups (to all ART), the media (for whom it makes good stories) and the public. Trying to balance the interest of these other players with those who take the risk and live with the consequences is probably the crucial factor in this current debate.

7 Mitochondrial (egg) donors.

7.1 This section considers the status of the mitochondrial donor to the resulting child. This is important because the discourse now is likely to determine any subsequent relationship.

7.2 This treatment will be regulated under the HFEAct and thus the discussion about the status of the mitochondrial donor has so far been considered in the context with which the HFEA is familiar i.e. the donation of an intact egg for fertility treatment. Since the mitochondrial donor will not be contributing to genetic material that relates to the characteristics of the child but to their health and wellbeing, it might be more appropriate to consider the donor to have a similar status to that of a living organ or blood donor.

7.3 The implications of considering the mitochondrial donor to be equivalent to the intact egg donor also relates to the process of documentation and central databases. Documentation about the 'intact egg donor' is appropriately analogous

to adoption with central databases and regulated access. Documentation about tissue and organ donation is traceable but held in individual medical records. Access to information is guided by good practice not regulators.[17]

[17] In this context it is relevant to note that there is ongoing legal debate about the current HFEA practice of retaining identifying information about those having relevant treatment that does not result in a child. At present every couple that start an IVF treatment have their identifying information retained by the HFEA irrespective of the outcome. This includes gamete donors. Thus if the mitochondrial donor is considered in the same manner as the intact egg donor, their identifiable information will be retained in the HFEA database even if there is no resulting child. There are probably human rights issues here.