EMJ EUROPEAN MEDICAL JOURNAL

REPRODUCTIVE HEALTH

EMJ Repro Health. 2019 Suppl 2 • europeanmedical-journal.com

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Cryos Symposium on Assisted Reproductive Technology

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This symposium took place on 3rd May 2019 in Aarhus, Denmark

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Disclosure: The speakers were paid by Cryos to present at this symposium. Mr Schou is the founder of Cryos. Dr Nielsen is an employee of Cryos and Dr Madsen is a former employee of Cryos. Prof Harper is a partner in the Embryology and PGD Academy, as well as CEO and founder of Global Women Connected, FemTech, Salve Tech (Merck startup), Cook Medical, and Gedeon Richter Plc. Mrs Kasiri is Director of European Operations at Cryos. Prof Humaidan reports honoraria for lectures and has received unrestricted research grants from Merck, Merck Sharp & Dohme (MSD), IBSA, Gedeon Richter Plc, and Ferring Pharmaceuticals. Prof Pacey has, in the last 2 years, been a receipt of income from grants, commercial contracts, and donations from the British Broadcasting Corporation (BBC), Cambridge Nutraceuticals Ltd, the Medical Research Council (MRC), Ferring Pharmaceuticals, Merck Serono Ltd, the National Institute for Health and Care Excellence (NICE), Origio Ltd, Precision Diagnostics GmbH, and the World Health Organization (WHO). All money was donated to the University of Sheffield to support research and training. Prof Golombok has received funding from the Wellcome Trust. Prof Ombelet, Prof Ory, Dr Shenfield, and Ms Grønbæk have declared no conflicts of interest.

Acknowledgements: Medical writing assistance was provided by Else Marie Kahr Thomsen.

Support: The Cryos Symposium and this article were funded by Cryos. The views expressed by the speakers are their own and do not necessarily represent the views of Cryos.

Citation: EMJ Repro Health. 2019;5[Suppl 2]:2-9.

Meeting Summary

The Cryos Symposium took place on 3rd May 2019 in Aarhus, Denmark, and gave the invited audience from all over the world the latest news and scientific research within the field of assisted reproductive technology. Experts gave educational lectures on important topics within ethics, legislation and donor children, donor sperm and eggs, and genetics, which are the main focus areas of the Cryos International Sperm and Egg Bank.

The first speaker was Dr Françoise Shenfield from University College London, London, UK, on ethics and cross-border reproductive care. Next was Prof Susan Golombok, University of Cambridge, Cambridge, UK, who spoke about mother–child relationships and children's psychological adjustment, which was followed by Ms Emma Grønbæk, a 22-year-old student from Aarhus, Denmark, who shared the personal story of her life as a donor child. Prof Steven J. Ory, Florida International University, Miami, Florida, USA, then presented the International Federation of Fertility Societies' Surveillance (IFFS) 2019 report: Global Trends in Reproductive Policy and Practice, 8th edition, followed by Mr Ole Schou, the founder of Cryos, who talked about the legal right of every child to know his or her legal parents and spoke of the necessity to change the United Nations Convention on the Rights of the Child. Male infertility was next on the agenda, as Prof Allan Pacey, University of Sheffield, Sheffield, UK, listed five important points to take into consideration regarding male infertility. One of the points raised was the prevalence of sexually transmitted infections, such as human papilloma virus (HPV), which set the stage for Prof Willem Ombelet, Genk & Hasselt Institute for Fertility Technology, Genk, Belgium, to give his lecture on his book titled 'Intra-Uterine Donor Insemination: Evidence-Based Guidelines for Daily Practice, 1st edition.' Prof Peter Humaidan, The Fertility Clinic, Skive Regional Hospital, Skive, Denmark, gave his lecture on the many exciting aspects associated with egg freezing, and the Director of European Operations in Cryos, Mrs Saghar Kasiri, talked about the advantages and disadvantages of frozen versus fresh eggs. Prof Joyce Harper, University College London, London, UK, brought up the fact that at least 24 million people around the globe have researched their family tree using online DNA testing databases, leading on to a lecture on genetic screening programme developments within gamete banks by Dr Lone Bruhn Madsen and Lead Clinical Geneticist Dr Henriette Roed Nielsen from Cryos. The symposium ended with Prof Wybo Dondorp, Maastricht University, Maastricht, Netherlands, giving a lecture on expanded genetic carrier screening.

Introduction

Cryos' own CEO, Peter Reeslev, welcomed the audience and quickly handed over the stage to Dr Françoise Shenfield from University College London, London, UK, who spoke about ethics and cross-border reproductive care. Her first note to her colleagues in the audience was to give thought to the use of the word 'tourism' in relation to women travelling abroad to receive help getting pregnant. Tourism, as she emphasised, has connotations relating to doing something for fun, and so the term stigmatises people seeking medical assistance. The reasons for seeking assistance abroad, in most cases, fall under one of two categories: legal restrictions, such as the procedure (or the recipient's relationship status) being illegal in their home country, or treatment availability or waiting list duration. Dr Shenfield pointed out, however, that there are many advantages for the patient, including their increased autonomous choice of treatments, access to foreign expertise, and, in some instances, quicker and cheaper treatment options abroad. This must, however, be balanced against the potential negative effects: the distance from one's support system at home, or the danger of multiple pregnancies for the recipient, surrogate, and future children. This could also cause the displacement of already scarce health resources to wealthy, foreign patients, especially in low income countries where there is also the risk of exploitation of egg donors or surrogates. There are also legal ambiguities surrounding the conception of children through international arrangements.[1]

Dr Shenfield also covered a series of research regarding oocyte donors' reasons for donating.

Altruism is the main reason in Belgium, Finland, and France, while reasons are more financially motivated in Greece, Russia, and Ukraine. A combination of both is seen in the Czech Republic, Ukraine, and Spain.[1] Not all countries compensate donors, and compensation is limited in Europe, but the proportionality of the compensation is an essential feature to ensure financial inducement does not negate the consent of the collaborators.[1]

Prof Susan Golombok, University of Cambridge, Cambridge, UK, was next to take the stage to talk to the audience about the choice to become a single mother, mother–child relationships, and children's psychological adjustment in this context. Prof Golombok gave the audience a perspective into the average experiences of single mothers by choice.

Many of these mothers would have preferred to start their family with a partner; however, they felt that if they wanted to have a child there was little choice. Most hoped to have a partner in the future. The survey also revealed that the average single mother is often well-educated, financially secure, and a professional who puts long consideration into their decision to become a single mother.[2] They often have concerns about their child not having a father and are worried about the children's feelings regarding being donor-conceived.[3]

Tell the Child the Truth

So, how does a child by an elective single mother develop in life? Studies of families created by single mothers by choice tell us not just whether children need fathers, but whether children need to know who their father is. Children of single mothers by choice are just as likely to have good relationships with their mothers, and be equally as well-adjusted, as children with both a mother and a father. Findings show that fathers are not essential for children's wellbeing.[4] However, the children's interest in their father from as early as 2 years old, together with the finding that they are more likely to desire to contact their sperm donor than children in different household structures, show that knowing the identity of their biological father is important for many children of single mothers by choice.[5,6]

Prof Golombok's findings about honesty were warmly supported by 22-year-old Ms Emma Grønbæk, a Danish nursing student. She provided the audience with a first-hand perspective of life as a donor-conceived child with the help of an anonymous donor. She was aware of her background from a very early stage in life and her family talked to her about her donor with warmth and gratefulness. Ms Grønbæk has, however, never felt the need to meet her donor. She has always felt that she has a father, a mother, and a family, and that that is enough for her.[3]

Prof Steven J. Ory, Florida International University, Florida, USA, was next onto the stage to present his findings from the IFFS 2019 report: Global Trends in Reproductive Policy and Practice, 8th edition, which did not uncover any countries that expressly prohibit cryopreservation of gametes or pre-implantation of embryos for fertility treatment or for fertility preservation, performed for medical or other indications. Approximately 65–80% of respondent countries noted the existence of laws, regulations, agency oversight, or professional guidelines that provided governance.[7]

However, there is extensive variation among countries in terms of which practices are regulated and how they are regulated. Prof Ory noted that gamete and embryo donation are well established practices and used by a large majority of countries and that >60% of countries expressly permit, and none prohibit, sperm, oocyte, or embryo donation. In contrast, *de novo* (donor egg and sperm) embryo donation is less commonly accepted and only available in 25–35% of countries.

The founder of Cryos, Mr Ole Schou, took the audience through some of his thoughts regarding parental rights and the importance of being clear as to who is the legal parent of the child, for instance with social parents, foster parents, or biological parents. This is particularly relevant in Denmark, where there are currently 37 official family types and a rising number of fertility treatments from third party donors.[8] This calls upon clear international rules, because every child has the right to have his or her legal parents defined. Mr Schou pointed out that the 1989 United Nations Convention on the Rights of the Child does not define anything about legal parents[9] and that he would like the fertility industry to demand an amendment to the convention so

that all children get a chance to have at least one legal parent.

A Man's Problem?

Male infertility was next on the agenda, a theme that was presented by Prof Allan Pacey, University of Sheffield, Sheffield, UK. He listed five important reasons to take into account when considering male infertility and a potential male fertility crisis, evident from the fact that 30–50% of fertility problems arise from the male partner:[10]

1. Declining sperm count has been widely reported.[11]
2. Modern couples are attempting to conceive children at older ages.[12]
3. The number of sexually transmitted infections are increasing within the population.[13]
4. More incidences of cancer are occurring, e.g., testicular cancer. [14]
5. Young men do not seem to be having as much sex as before, potentially due to the use of videogames and streaming services.[15]

Prof Pacey stated that we could be looking at the wrong themes when trying to help the men; there is insufficient evidence to conclude that exposure to heat, be it occupational or as a result of clothing or body position, affect semen quality and male fertility.[16] There is some evidence to suggest negative effects of cigarette smoking on semen quality, but not all studies support this.[16] However, as smoking has an adverse effect on general health and wellbeing, it is recommended that men trying for a pregnancy should abstain from smoking. Evidence supports a detrimental effect of obesity on many aspects of health; however, evidence is conflicting about a potential effect on reproductive function.[17-20] Males presenting for fertility evaluation should be counselled about weight-loss strategies when their BMI and waist circumference data demonstrate obesity, especially in cases of morbid obesity.

Sexually transmitted infections, such as HPV, were discussed by Prof Willem Ombelet, Genk & Hasselt Institute for Fertility Technology, Genk, Belgium, who gave his lecture on his book titled 'Intra-Uterine Donor Insemination: Evidence-Based Guidelines for Daily Practice, 1st edition.' He stated that HPV will be an important theme in the years to come, also in terms of obtaining pregnancy, as HPV positivity in women and men undergoing intrauterine insemination has a negative effect on pregnancy rates.[21]

He went through his findings regarding how to obtain pregnancy, highlighting that key to this goal is to get a proper female diagnosis taking into consideration the history of the woman through a clinical examination, hysterosalpingography, vaginal ultrasound, hysteroscopy, and blood sample or cervical smear.

His conclusion was that the most important factor was the age of the woman, but a study has also shown that it matters how the insemination is performed. If the insemination is conducted by somebody (clinical assistant or doctor) who does not have enough time and who works in an unfriendly manner, the pregnancy rates are significantly lower compared to if it is conducted by a midwife or somebody who performs the insemination more slowly (a few minutes instead of a few seconds) and with less stress involved.[6]

What Waits Ahead?

Prof Peter Humaidan, The Fertility Clinic, Skive Regional Hospital, Skive, Denmark, took the audience through some of the possibilities that accompany new technologies and the risks connected to assisted reproductive technology in his presentation titled 'Freeze All – For All?'

Singleton mothers giving birth after frozen embryo transfer have an increased risk of intrauterine overgrowth,[22] hypertensive disorders,[23] preeclampsia in the mother,[24] increased cardiovascular morbidity in adult offspring,[25] and long-term morbidity.[25]

Opdahl et al.[23] compared the risk of hypertensive disorders in pregnancy following assisted reproductive procedures with the risk of hypertensive disorders following a spontaneously conceived pregnancy. The highest risk in singleton pregnancies was seen after frozen-thawed cycles (risk: 7.0%; risk difference: 1.8%; 95% confidence interval: 1.2–2.8). Comparing twin pregnancies, the risk was higher after frozen-thawed cycles (risk: 19.6%; risk difference: 5.1%; 95% confidence interval: 3.0–7.1)

and there were no clear differences in risk with *in vitro* fertilisation and intracytoplasmic sperm injection.[23]

Prof Humaidan also talked about the future aspects of oocyte donation that provide hope for many patients. In Denmark, approximately 1,100 oocyte donation cycles are performed yearly. This gives reason to consider the ethical implications surrounding the procedure; for instance, the opportunity for women choosing to become mothers at a very late age because it is possible to preserve their eggs. In the future, it may become possible to delay menopause to reduce osteoporosis, three dimensionally (3D) print an artificial ovary, or preserve human ovarian tissue for cryopreservation and subsequent usage later in life. Fertility preservation for cancer patients is already an option in Denmark and, to date, 17 children have been born using this method, in which ovarian tissue is re-transplanted in cancer survivors who had one ovary removed prior to chemo or radiation therapy.[26] Prof Humaidan concluded his lecture by stating that major ethical questions will develop in the future alongside new scientific developments within the field of assisted reproduction.

Next, the Director of European Operations in Cryos, Saghar Kasiri, compared fresh and frozen eggs in terms of advantages and disadvantages, and gave the audience a thorough look into the egg donor recruitment process after reminding them that the first birth following successful frozen egg donation treatment happened in 1986.

The Cryos donor requirements are for the individual to be 18–32 years old, well-educated, and to be healthy. All donors go through extensive screening with regard to their mental health, reasons for donating, and medical and family history. Only 4% of applicants end up donating.

There is not a large difference between live birth or miscarriage rates between fresh and frozen eggs. An advantage of using fresh donor eggs is that, in most cases, all the eggs retrieved go to the recipient. Other advantages include the fact that there are usually a high number of oocytes, leading to increased numbers of developed embryos for cryopreservation. Additionally, costs are higher for vitrified cycles but lower for subsequent thaw cycles. The disadvantages of using fresh donor eggs are time, since it takes a minimum of 3 months to 1 year from donor selection to embryo transfer; difficulties regarding the synchronisation of donor and recipients that may result in cycle cancelation; donor liability issues, for instance when the donor is not taking their medication correctly, or manifest empty follicle syndrome, ovarian hyperstimulation, or other complications; and regulatory compliance and high costs. The advantages of using frozen donor eggs include convenience, since there is no need to synchronise donor and recipient cycles; lab schedule; the larger selection of donors; and the lack of concern over empty follicle syndrome. Success due to recent advances in cryobiology and embryo culture have also increased live birth rates to almost equal those of fresh donor eggs,[27] and at first attempt the cost is lower than that for fresh donor eggs. The disadvantages of using frozen donor eggs include the smaller number of eggs (cohort of 6–8 eggs), particularly regarding the fact that most women needing frozen egg donation are of advanced age and therefore would like one or two children, meaning fewer embryos are retained for cryopreservation; the technically challenging nature of warming oocytes, although Cryos does provide full training to clinics; and cost, because while the initial cost is lower, there are fewer embryos created and thus fewer being cryopreserved. The cost of transferring a frozen embryo is far cheaper than doing another frozen donor egg cycle to have a sibling or to repeat *in vitro* fertilisation if the cycle fails.[8]

Success rates using frozen donor eggs are dependent on several factors, such as the quality of the donor eggs, the ability to perform effective freezing and thawing of the eggs, the number of eggs thawed and embryos produced, and the expertise and quality of the *in vitro* fertilisation, embryo development, and egg guarantee programmes.[28] The cost of the two technologies is almost the same in Europe; however, in the USA the first egg donation treatment with frozen donor eggs is cheaper than with fresh ones.

Donor Anonymity as a Major Theme

Donor anonymity and genetic testing was a major theme of the symposium and was discussed by Prof Joyce Harper, University College London, London, UK, who highlighted the fact that at least 24 million people around the globe have researched their family tree using online DNA testing databases.[29] Four major companies share the market, including 23andMe and Ancestry DNA. There are numerous reports of donor-conceived individuals looking for half siblings or even their donor. Even if the donor has chosen to be anonymous and not contributed their DNA to a database, there have been cases where donor- conceived individuals have managed to trace their donor via these services. If relatives, including uncles, aunts, and cousins, have added their DNA to the database and built an online family tree, it is possible for donors to be traced. Some children have inadvertently discovered that they do not have the parents they expected because they are donor-conceived and had not been told. The use of this technology means that anonymity can no longer be guaranteed.

Unless their parents disclose to them, donor-conceived children may never learn of their true birth origins, as information about their true biological parents is not recorded on the birth certificate. It is, however, possible for many to find out their background through DNA testing. Donor-conceived people may have many half siblings as a result of the same person's donations. Some sperm donation is unregulated via online sites where donors and women can meet. Some of these donors have said they have produced up to 800 children. Prof Harper asked the audience a rhetorical question: "Would you want your child to have 799 siblings?" It is most likely that no one would say yes to that.

With the increased use of DNA testing, and the possibility of children finding out about their genetic origins, it is important to be honest with donor-conceived children. People working in the field should encourage parents to talk to their donor-conceived children because no one should find out information as sensitive as this by accident.

Finding out by accident: words that led swiftly to the next lecture regarding genetic screening programme developments within gamete banks by Dr Lone Bruhn Madsen and Lead Clinical Geneticist Dr Henriette Roed Nielsen, from Cryos. Dr Madsen stated that there is a need for an international screening standard, as all humans carry several genetic diseases and are predisposed to various genetic conditions. Gamete donors at sperm and egg banks are currently assessed prior to acceptance through a thorough evaluation of donors' personal and family medical history to screen for the risk of potential inherited diseases like cystic fibrosis. Cryos test for 46 diseases and always advise donors to talk to their own families if anything is found in their donation. Moreover, it is common for gamete donor banks to perform karyotyping and to screen for a variable number of autosomal recessive diseases, using carrier screening to identify and reduce the incidence of a limited number of recessive diseases. It will, however, still not be possible to avoid genetic diseases in donor-conceived offspring. When a donor is blocked because of a hereditary condition, it is necessary to provide genetic counselling for the recipients and offspring. Implications of the condition depend on both the recipient's situation and the type of transmission.

Dr Nielsen gave her recommendation for when it is relevant to provide genetic counselling for the recipients and their offspring, including being honest regarding both diseases and the fact that the coming child could be interested in knowing about their donor.

Additionally, there is an increasing tendency in the general population towards the direction of more genetic screening, and this, of course, also impacts on gamete donor banks. The 'AncestryDNA' kit was one of the top five most purchased products on Amazon for Black Friday and Cyber Monday in 2018.[30]

The Right Reason to Test

Should we be using pre-conception genetic tests in gamete donation programmes? Prof Wybo Dondorp, Maastricht University, Maastricht, Netherlands, believes so, albeit under certain conditions, and presented his case in his lecture on expanded genetic carrier

screening, detailing what is at stake, the advantages and drawbacks, and applying expanded carrier screening.

In addition to the medical and family history that is always taken, genetic testing of donors should also be implemented. Some argue that there is no good reason for genetic testing, as donor conception does not have to be safer than reproduction between partners. However, this ignores morally relevant differences between these contexts. On the other hand, making donor conception slightly safer is not the only morally relevant consideration. There is a trade-off between benefits (a small increase in safety) and drawbacks for the recipients (higher costs affecting access, draining the donor pool), but possibly also for the donors who may be confronted with difficult-to-handle test results.

Testing should be proportional. An interesting proposition in this regard is expanded universal carrier screening for autosomal recessive disorders.[31] As this would entail genetic matching between donors and recipients, it would not lead to excluding donors. It will, however, raise costs for recipients and produce barriers for some. Moreover, imposing testing and matching upon recipients seems difficult to justify in light of the autonomy aim of reproductive screening. Expanded universal carrier screening as an option for recipients accepting higher costs may well be justified, depending on a carefully selected gene panel, to avoid outcomes with possible psychosocial drawbacks.[32]

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