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EDITORIAL

J DOHaD issue on ART and DOHaD

We are very pleased to introduce a special themed issue of *Journal of DOHaD* where a series of papers collectively consider the current practices and technologies associated with assisted reproductive treatments (ART) to overcome human infertility but with a perspective on this journal's central concept of the 'Developmental Origins of Health and Disease'.

The progress made in IVF and ART since its inception as a clinical procedure almost exactly 40 years ago can only be described as remarkable, many millions of apparently healthy children have been born worldwide that otherwise would not have existed and some now reaching early middle age. For those millions, the chance of life, and indeed *existence* in its true sense, must be credited to the pioneers and practitioners of ART over several decades, with the deserved accolade of the Nobel Prize in Physiology/Medicine to Professor Bob Edwards in 2010 for the development of IVF. For these children, and the reward of overcoming infertility and raising a family by their parents, ART has been a fantastic global success. Technologies and practices, both clinical and in the laboratory, continue to be refined to maintain and extend that success. Yet, ART has its hurdles to overcome – live birth rates per treatment cycle have remained stubbornly low over the years but are gradually increasing (around 25%),[1] reflecting the difficulty of creating and selecting embryos with good potential despite many technological advances. Similarly, there are concerns of multiple pregnancy risk if more than one embryo is transferred. Understanding the 'biology' of gametes, embryos and the maternal reproductive tract offer ways forward in this struggle for improved outcomes – but then there is DOHaD.

Readers of this journal will not need an introduction to the DOHaD concept. That there is a relationship between our health and physiology as adults and our experience *in utero* decades earlier has been substantiated across different world populations and in historical records from human famines. Healthy diet during pregnancy, avoiding malnutrition (both over- and under-nutrition) is recommended to protect against chronic disease risk in offspring later life. However, here comes the rub – research investigating the interface between maternal (and paternal) environment on conceptus development and potential in the DOHaD context has increasingly pointed towards the period around conception as the vulnerable window when adverse programming may initiate.[2,3] Although such studies commonly use *in vivo* animal nutritional models, *in vitro* treatments of gametes and preimplantation embryos also show consequences for health in later life. Moreover, epidemiological studies on IVF children and growing adults together with animal studies mimicking directly ART conditions and treatments show increased risk of cardio-metabolic comorbidities in the next generation.[4,5] This 'periconceptional' vulnerability appears to derive from environmental factors causing interference with, or inducing adaptation within, inherent reproductive mechanisms such as the epigenetic reprogramming of the new embryonic genome, the setting of metabolic homeostasis in the embryo including mitochondrial legacy, or the regulation of early cell lineage diversification.

The interface between ART and DOHaD in this issue covers five reviews. The paper by David Gardner and Rebecca Kelley from the University of Melbourne[6] focuses on the impact environmental conditions of the IVF laboratory may have on human embryos and how combinations of such factors, together with patient demographics, may influence embryo phenotype. Miaoxin Chen and Leonie K. Heilbronn from the Tongji University School of Medicine in Shanghai[7] then review the evidence for health outcomes, both short- and long-term, for ART children into adulthood and consider potential mechanisms and future protective strategies. Next, Sky Feuer and Paulo Rinaudo from the University of California in San Francisco[8] extend this evidence for ART-mediated effects using mouse models for underlying physiological, metabolic and transcriptional mechanisms affecting postnatal phenotype. The paper by Marc-Andre Sirard from the Université Laval, Québec,[9] then examines the bovine model to consider the influence of ART techniques on embryo epigenetics and their potential long-term consequences. The paper by Marie-Christine Roy, Charles Dupras and Vardit Ravitsky from the University of Montreal[10] considers the ethical issues raised by the epigenetic risks associated with ART to patients and includes a call for professional societies to generate guidelines for clinicians and practitioners on such risks. Lastly, the paper by Michael Davies, Alice Rumbold and Vivienne Moore from the University of Adelaide[11] considers the impact of changing technologies in ART over time on perinatal outcomes, with reference particularly to the South Australian Birth Cohort of some 300,000 deliveries, and concludes that more follow-up studies are necessary to ensure safety in ART policy.

Collectively, these articles form a synthesis of current understanding of the interface between ART and DOHaD and provide a foundation for future strategies, based upon biological and clinical evidence, for improving the safety of ART for long-term health. We hope readers will find them a timely and informative series.

References

1. Human Fertilisation and Embryology Authority. Fertility treatment 2014 Trends and figures. HFEA.
2. Fleming TP, Velazquez MA, Eckert JJ. Embryos, DOHaD and David Barker. *J Dev Orig Health Dis*. 2015; 8, 1–7.
3. Sinclair KD, Watkins AJ. Parental diet, pregnancy outcomes and offspring health: metabolic determinants in developing oocytes and embryos. *Reprod Fertil Dev*. 2013; 26, 99–114.

4. Guo XY, Liu XM, Jin L, Wang TT, Ullah K, Sheng JZ, Huang HF. Cardiovascular and metabolic profiles of offspring conceived by assisted reproductive technologies: a systematic review and meta-analysis. *Fertil Steril*. 2017; 107, 622–631.
5. Hart R, Norman RJ. The longer-term health outcomes for children born as a result of IVF treatment: Part I – general health outcomes. *Hum Reprod Update*. 2013; 19, 232–243.
6. Gardner D, Kelley R. Impact of the IVF laboratory environment on human preimplantation embryo phenotype. *J Dev Orig Health Dis*. 2017; 8, 418–435.
7. Chen M, Heilbronn LK. The health outcomes of human offspring conceived by assisted reproductive technologies (ART). *J Dev Orig Health Dis*. 2017; 8, 388–402.
8. Feuer S, Rinaudo P. Physiological, metabolic, and transcriptional postnatal phenotypes of in vitro fertilization (IVF) in the mouse. *J Dev Orig Health Dis*. 2017; 8, 403–410.
9. Sirard M-A. The influence of in vitro fertilization and embryo culture on the embryo epigenetic constituents and the possible consequences in the bovine model. *J Dev Orig Health Dis*. 2017; 8, 411–417.
10. Roy M-C, Dupras C, Ravitsky V. The epigenetic effects of Assisted Reproductive Technologies: Ethical considerations. *J Dev Orig Health Dis*. 2017; 8, 436–442.
11. Davies M, Rumbold A, Moore V. Assisted reproductive technologies: A hierarchy of risks for conception, pregnancy outcomes, and treatment decisions. *J Dev Orig Health Dis*. 2017; 8, 443–447.

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Guest Editors