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EC GYNAECOLOGY
Editorial

Assisted Reproductive Technology: Current Problems and Challenges

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Received: April 22, 2019; **Published:** April 30, 2019

Keywords: *Assisted Reproduction; In-vitro Fertilisation; Intracytoplasmic Sperm Injection; Offspring Abnormalities; Parent-to-Offspring Disease Transmission; Epigenetics; DNA Methylation; Non-coding RNAs*

Abbreviations

ART: Assisted Reproductive Technology; IVF: *In-vitro* Fertilisation; ICSI: Intracytoplasmic Sperm Injection

When the first birth after *in vitro* fertilization (IVF) was reported [1], the technique was considered highly innovative, scientifically and medically interesting, but limited as to its indications in the field of human infertility treatment. In fact, during the first years of its use, the indication of IVF was limited to the treatment of female infertility due to fallopian tube obstruction [2]. Fourty years after, IVF and IVF-derived techniques, collectively termed assisted reproductive technology (ART), have progressively become a solution for most types of both female and male infertility, and are increasingly being used even outside the field of infertility treatment, to control the parent-to-offspring transmission of a variety of genetic diseases [3].

However, the wide use of ART in different clinical indications raised some new issues, concerning the impact of different ART methods on both the mother [4] and offspring [5,6] health. Accordingly, some of these issues are related to different pathological conditions, underlying infertility of one or both parents. In these cases, the use of ART is a necessary prerequisite to achieve pregnancy and childbirth and can thus hardly be blamed as the main causative factor. However, these situations represent a challenge for future research to limit negative consequences of the parents´ pathologies on the ART outcomes. On the other hand, some data suggest that ART interventions themselves can be at the origin of an increased risk for mother and child. In fact, both patient-related and technique-related causes actually appear to be involved in most cases, since a particular clinical condition of the parents requires the use of a patient-tailored therapeutic solution, which is not always the case in the current ART programmes, often tending to standardise, rather than customise, the ART protocols [7,8].

Parent-related issues

Apart from gene deletions and/or mutations in one of the parents, whose transmission can be avoided by selection of unaffected embryos using preimplantation genetic testing, there are some pathological conditions that can be transmitted from the parents to the offspring via epigenetic mechanisms. This type of "soft" inheritance, as opposed to the "hard" (genetic) inheritance, has been shown to mediate parent-to-offspring transmission of metabolic diseases, such as obesity [9,10] or diabetes [11,12] and the susceptibility to different types of cancer [13,14]. As opposed to genetic abnormalities, epigenetic defects are much more difficult to diagnose and to treat. Research projects are in course to detect epigenetic abnormalities in liquid biopsy samples (blood, follicular fluid, seminal plasma) from patients at risk [15].

In spite of the fact that most of the epigenetic information present in parental cells is erased in mammals during germline- and early zygotic epigenetic reprogramming, mainly based on genome-wide DNA demethylation, some loci can resist this global process due to the action of different factors, including small non-coding RNAs, factors preventing DNA demethylation and those regulating the acetylation status of histones and other DNA-associated proteins [16]. Consequently, different epigenetic traits acquired by the parents can be transmitted to offspring via gametes at fertilisation. ART is likely to promote this type of transmission by facilitating reproduction of persons who, owing to different underlying pathologies, might be less likely to procreate spontaneously. Even though neither genetic nor epigenetic abnormalities detected in preimplantation embryos can be treated reliably nowadays, the affected embryos can be cryopreserved until the clinical validation of appropriate methods for their correction, hopefully in a relatively near future [17].

Technique-related issues

As early as mid-1990s, it was noted that children conceived by intracytoplasmic sperm injection (ICSI) had an increased risk of sex chromosome abnormalities as compared with naturally conceived ones [18]. Though the parental inheritance was suggested as the most probable cause [18], the suspicion that these abnormalities can be due, in some cases, to the ICSI technique itself was immediately raised [19]. It was suspected that abnormalities of sperm-induced oocyte activation after ICSI, as compared with natural fertilization [20], might cause irregularities of the subsequent embryonic cell divisions leading to aneuploidy [19].

Other data suggest that technique-related problems may be associated not only with ICSI but with conventional IVF as well. For instance, both conventional IVF and ICSI were reported to increase the risk of certain types of birth defects in general [21-23] and heart defects in particular [24,25]. Even though some of these defects might be partly due to the trend towards multiple pregnancies and a higher maternal age in ART cases as compared with natural conception, a negative impact of ART on the offspring health can still be detected even after statistical corrections for these potentially negative factors [5].

Given the fact that there does not appear to exist a significant difference between the children conceived by conventional IVF and by ICSI [26,27], the problems arising from different ART techniques appear to be associated with their common feature - the exposure of gametes and early embryos to *in-vitro* environment which, in spite of the continuously increasing quality of culture conditions, does not accurately mimic that of the natural site of fertilization and preimplantation development within the human oviduct. It was suggested that the formulation of the currently used IVF media is still not optimal to provide zygotes and early cleaving embryos with an appropriate protection against excessive DNA demethylation whose consequences cannot be detected before embryo transfer but yet can influence negatively further embryonic, fetal and offspring development [28].

Synthetic view: Towards patient-tailored ART

Careful analysis of the current problems with ART, as outlined above, shows that the parent-borne and the technique-borne issues are indissolubly linked to each other. The best possible solution is likely to be a synthetic one, converting ART from being part of the problem into its solution. This will only be possible if we abandon all kinds of generalisation and begin to consider each case as a unique pathological entity in order to adapt the techniques to be used to the individual condition of each patient. Some recently published studies reflect this change of mentality [28,29]. Let us hope that the fruit will not take too much time to ripen.

Conflict of Interest

There is no conflict of interest in relation with this study.

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Volume 8 Issue 5 May 2019