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Opinion

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National Assisted Reproductive Technology Registers: Questions and Answers

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Abstract

We analyzed some parameters, affecting the success rates of in vitro procedures taken from the national registers of Japan, China, and the USA. We compare birth rates for frozen embryo transfer (FET) and fresh ET after IVF / ICSI procedures, and we believe one of the reasons for the higher FET success rate is the "therapeutic" effect on embryos following the freezing / thawing procedure. This phenomenon has been described in our "Theory about the Embryo Cryo-Treatment". We believe that cryopreservation helps to partially eliminate the negative impact of air pollution caused by the pollution of the environment on the development and implantation of embryos.

Keywords: National registers, Delivery rate, Pollution, FET, FreshET

Opinion

As you know, the first application and main indication of embryo freezing is for storage purposes. Other reasons as to why we freeze embryos and do not switch to fresh embryo transfer (ET) are: OHSS risk, significant increase in progesterone on the day of HCG administration during stimulation (progesterone levels above 1.5 ng/ml and above 1 ng/ml in patients in advanced reproductive age are associated with lower success rates with fresh ET), need for genetic screening, low responders, inadequacy of the cervix, requiring hysteroscopy or implantation window (ERA test), and so on. On the other hand, there has been a significant increase in the success rate of frozen embryo transfer (FET) compared to fresh ET and a number of clinics have begun to implement the "Freeze-all" policy, i.e. they do not perform ET in the stimulated cycle, but rather freeze all embryos. In a subsequent or later cycle, with or without HRT, the embryos are thawed and ET is performed.

Another interesting fact supporting the increased success rate of frozen ET is data from the Japanese National Registry on the number of ART procedures and their success rate based on births. A summary report for 2017 by the Ethics Committee of the Japan Society of Obstetrics and Gynecology" by Ishihara et al. [1], which analyzes the current status of assisted reproductive technology (ART) service in Japan. This data from Japanese National Registry shows that the delivery rates for IVF/ICSI fresh ET and FET were 16.2%, 13.2% and 24.2%, respectively. Looking at statistics, we shall find that delivery rate in FET cases have increased about 60 %, compared with fresh ET after IVF/ICSI procedures.

We find a similar average increase of success rate of FET, compared with fresh ET of IVF/ICSI in data from the mainland China for 2016 - IVF/ICSI/FET were 18.7%, 16.7% and 37.6% and National Report of SART for 2017: 42.2% FET vs IVF/ICSI 28.9%, respectively. This means an increase of delivery rate of FET more than two times in China and for the USA there was an increase of delivery rate, using FET of 42% on the base of delivery [2,3].

Analyzing the results of increasing success rate of FET, compared with fresh ET IVF/ICSI on the base of delivery, a question arises: What are the reasons and biological mechanisms of that increase?

It is a well-known fact that different factors from the environment affect oocytes and embryos. Air quality is one of the reasons when pregnancy rates decline. Volatile organic compounds (VOCs) are very harmful to embryo development [4]. During embryonic cleavage, VOCs directly attach to DNA and abort growth [5,6] Lot of studies find that small amounts of VOCs in the air of an

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IVF laboratory can have detrimental effects on pregnancy rates [7, 8].

Other, a majority of IVF labs are located in urban areas with high level of air pollution. This causes two general types of pollutants inside in the IVF laboratories: particulate matters (PM) and VOCs. The conditions in IVF laboratories have been proven to be related to the outside humidity and air temperature, which has a profound impact on the embryo's development and implantation rates [9,10]. On the other hand, regardless of the high-end modern purification systems, VOCs have the ability to interact with PM, because they have been proven to be difficult to remove from the laboratories' air [11]. How does this affect embryo development?

Air pollution can generate reactive oxygen and nitrogen species [12]. Those particles may generate radicals via a Fenton reaction in the presence of metals, like iron [13]. A possible source of ROS production is through the PM-induced altered functioning of NADPH oxidases, telomere-mitochondrial dysregulation [12,14]. One of the fundamental concepts identified with air contamination is the oxidative stress. Not many studies have related this in early human development with clinical results in pregnant patients [15]. Oxidative harm delivered by toxins has demonstrated time-dependent aggregate effects. It can influence the mitochondria's membrane potential or lead to apoptosis. Embryonic stem cells have demonstrated various other reactions when exposed to environmental toxins or antioxidant treatments, compared to somatic cells [16].

In our view, the explanation and mechanism of this significant increase in post-FET success is hypothesized to be the positive effect on implantation of freeze/thaw embryos presented in "Theory of Embryo Cryo Treatment" [17]. We believe that the one of reasons for this increasing in FET success rates compare fresh ET is the negative effect of air pollution, which is reflected in the lower implantation potential of the embryo in fresh ET.

What is the mechanism of such an influence on the embryos during freezing/thawing? According to the theory, "As a result of freezing or thawing of the embryos, there are reduced high levels of reactive oxygen species (ROS), detoxification of the cells is carried out, and the amount of mutated mtDNA is reduced." Cryopreservation will increase other ROS that are different and will activate of a hormetic response.

In conclusion, we believe that the freezing/thawing procedure has a „treatment" effect on the embryos, possibly eliminating the negative effects of a human-modified environment. Future research could give us answers as to whether there are other reasons for the higher average FET success rate and for which patient groups the "freeze all" strategy is appropriate.

We would like to make some clarifications: this analysis does not include the summarized European IVF-monitoring Consortium (EIM) results for Europe [18], because according to the authors the aggregated data from various countries is with variable levels of completeness. Registries from a number of countries have failed to provide adequate data about the number of initiated cycles and deliveries. That is why the authors of the published data believe that the results should be interpreted with caution. The analysis does not also include Wang et al.'s results [19], concerning the effect of outdoor air pollution on post-FET and fresh ET results. In our opinion, the published results obtained on fresh ET with cleavage stage embryos should not be comparable with the results on the FET of the embryo in the blastocyst stage.

Disclosures

Conflict of interest

The authors declare no conflict of interest. Human and Animal Rights: This article does not contain any study with human or animal participants that have been performed by any of the authors.

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