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Editorial

Early Pregnancy Loss: Can It Be Attributed to IVF Laboratory Performance?

In most IVF clinics worldwide, infertility specialists and embryologists often engage in discussions regarding the increased rate of early pregnancy loss (EPL) in women who have undergone embryo transfer during a defined period. They are always asked whether any modifications to IVF laboratory protocols, equipment, materials, or culture media have contributed to the rise in EPL. Indeed, the performance quality of the embryology laboratory, the type of protocols, materials, as well as the expertise and experience of the embryologists have critical role in both the success of an IVF center and the incidence of EPL. It is important to emphasize that EPL should not be predominantly attributed to deficiencies in IVF laboratory performance. Although the causes of EPL are not fully understood, the most likely proposed factors include the quality of transferred embryos in IVF/ICSI cycles or endometrial dysfunction. Both parental factors, particularly maternal ones, significantly influence the risk of EPL. Maternal age, induction ovulation protocols, oocyte and embryo quality, endometrial receptivity, and uterine abnormalities are key factors that affect the progression of early pregnancy. In addition, paternal factors such as age and sperm quality also play a role in EPL, although maternal factors are often the main focus of research into its causes. Several studies consistently identify advanced maternal age as a significant independent risk factor for EPL following IVF and embryo transfer (ET). Specifically, the risk of EPL is 1.35 times higher in women aged 35-39 compared to those under 35 years, and 3.88 times higher in women aged 40 years and older. This increased risk is often attributed to the higher rate of oocyte aneuploidy in older women, with the oocyte aneuploidy rate reaching up to 70% in women over 35 (1).

Increased body mass index (BMI) is strongly associated with a higher likelihood of EPL even after singleton euploid embryo transfer. One study found that the miscarriage rate increased significantly with higher BMI (odds ratio 1.04). Non-chromosomal factors associated with obesity, such as metabolic, endocrine, inflammatory, and epigenetic mechanisms have been suggested as potential contributors. Weight loss before an IVF/ICSI cycle is proposed as a potential measure to reduce the risk of EPL (2). A history of miscarriage is another important factor in EPL. While some studies have found no association between the number of previous miscarriages and EPL, others have identified a history of spontaneous miscarriage as an important factor, particularly in younger women. Among women under 35 undergoing IVF/ICSI, a history of spontaneous miscarriage was identified as a significant risk factor for EPL. Additionally, recurrent pregnancy loss (RPL) is associated with increased rates of EPL in IVF/ICSI cycles (1).

Endometrial thickness at the time of embryo transfer has been shown to be an independent protective factor for the development of EPL. One study found that the risk of EPL was 0.78 times higher in women with an endometrial thickness ≥8.5 *mm* compared with women with an endometrial thickness <8.5 *mm*. The overall trend suggests that thicker endometrium is associated with better clinical outcomes and a lower risk of EPL. However, some studies have shown inconsistency considering this association. Chronic endometritis increases the risk of EPL even after antibiotic treatment. Moreover, a history of induced abortions is considered as a potential risk factor for early miscarriage, possibly due to endometrial injury as its consequence (1).

The type of controlled ovarian hyperstimulation (COH) protocol used during ovarian stimulation can also affect the risk of EPL. Studies have shown that GnRH antagonist and minimal stimulation protocols may be connected with a higher risk of EPL compared with a long GnRH agonist protocol. It is important to note that these factors can interact, and the risk of EPL is often multifactorial. In frozen-thawed embryo transfer (FET) cycles, the type of endometrial preparation protocol influences the risk of EPL. Natural cycle of embryo transfers was associated with a lower rate of EPL (0.73 times) compared with hormone replacement therapy (HRT) cycle. One study found that ovulation-induced FET cycles had a lower EPL rate than HRT cycles. The presence of a corpus luteum in natural or ovulation-induction cycles has been suggested as a possible explanation for these differences. The rate of EPL was significantly higher in HRT cycles compared with stimulated cycles (1, 3).

Embryo quality, assessed by factors such as morphology or blastomere number, has been shown to be a predictor of EPL, particularly in fresh cycles. A higher number of high-quality embryos was an independent protective factor for early miscarriage. The number of good-quality embryos was identified as an important factor that could reduce the risk of EPL in younger women (<35). The risk of EPL was significantly decreased

when the leading embryo had six to ten blastomeres compared with four to five blastomeres. Poor-quality embryos are more likely to have chromosomal abnormalities, metabolic defects, or mitochondrial dysfunction, leading to higher rates of early miscarriage. However, a study focusing on single euploid blastocyst transfer did not show any difference in clinical miscarriage rates between different embryo quality groups (high, normal, low, poor). This suggests that while embryo morphology predicts implantation, chromosomal composition (euploid status) may represent a more significant factor in the occurrence of EPL.

The use of machine learning in time-lapse imaging to predict the risk of miscarriage based on early embryonic developmental features is currently being investigated. Some studies have shown that transferring more than one embryo (*i.e.*, two embryos) is a protective factor with a lower risk of EPL compared with transferring a single embryo. Transferring two embryos was associated with a 29% reduced risk of EPL. In freeze-thaw cycles, the number of embryos transferred (*i.e.*, more than one embryo) was a protective factor for early miscarriage. However, another study focusing on frozen-thawed embryo transfer of morphologically good, day 5 blastocysts found that double embryo transfer (DET) was associated with increased clinical pregnancy loss compared to single embryo transfer (SET). Other studies have found no significant relationship between the number of embryos transferred and early miscarriages. Despite the possible reduction in miscar-riage rates with multiple embryos, limiting the number of embryos transferred is recommended due to the risks associated with multiple pregnancies (1, 4, 5).

The technique used for oocyte fertilization, whether conventional IVF or intracytoplasmic sperm injection (ICSI), does not seem to be a relevant factor for EPL. Sperm DNA fragmentation (DFI) is frequently assessed in the laboratory and has been linked to pregnancy outcomes. Some studies indicate that increased DFI is linked to an increased risk of EPL, although findings from different studies on this association have varied. The risk of EPL has been found to be significantly higher in frozen-thawed embryo transfer cycles compared to fresh embryo transfer cycles. One study reported a 1.48 times higher risk in frozen cycles. This might be attributed to the embryo freezing and thawing process, affecting the developmental potential of embryos. Although vitrification is considered safe, but the skills and consistency of laboratory operators in performing cryopreservation can influence the survival and developmental competence of thawed embryos (1, 2, 4).

Finally, EPL should not be absolutely attributed to factors related to the IVF laboratory performance. In fact, EPL is often multifactorial and some potential factors such as genetic factors (beyond aneuploidy), immune and systemic factors, environmental influences, and unhealthy lifestyle may not be fully identified or understood in retrospective studies due to their complexity. In addition, the results of most studies show variability or inconsistency, indicating the need for further large-scale prospective studies for validation.

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