REVIEW ARTICLE

Preembryo: Medical, Moral, and Legal Aspects

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Abstract

The preembryo refers to the early stage of human development following fertilization but before implantation in the uterus, typically up to about 14 days old. The moral status of the human preembryo is a subject of ethical and philosophical debate Some argue that the preembryo should be accorded full moral status and rights from the moment of fertilization, considering it as a human being. with the same moral values and rights as any other person. This perspective is often rooted in religious or philosophical beliefs that attribute personhood to the zygote, on the opposite end of the spectrum, some argue that the preembryo lacks moral status and that considerations about moral standing and rights are only applicable to more developed entities with consciousness and sentience. The legal status of preembryos is closely tied to regulations governing assisted reproductive technologies (ART) and embryonic research. In countries where embryonic research is allowed, the legal status of preembryos used for research purposes may be subject to specific regulations and oversight. These regulations often aim to strike a balance between advancing scientific knowledge and respecting ethical considerations. Recently stem cell research and developmental biology have opened up possibilities for generating synthetic gametes, also known as *in vitro* gametogenesis, which refers to the process of generating functional sperm and eggs outside of the human body through cellular reprogramming or other techniques. June 2023, the possibility of generating artificial embryos from stem cells. The aim is to understand early human development better and potentially use this knowledge to treat various medical conditions and advance reproductive technologies. The present scientific achievements create concern around the potential misuse of this technology, as well as questions about the moral status of these synthetic embryos and the implications for human life.

Keywords: Ethics, *In vitro* fertilization, Preembryo, Synthetic gametes and embryos.

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This paper has been previously published by Joseph G Schenker. Preembryo: medical, moral and legal aspects. In Kurjak A, Chervenak FA. Donald School Embryo as a Person and as a Patient. Jaypee Brothers, New Delhi, 2019:75–81. Preembryo is defined as the period from fertilization *in vivo* and *in vitro* until implantation. Fertilization is not a single event but it is an event that includes several steps.

Events of Fertilization

Following sperm entry into the oocyte, the male chromatin decondenses rapidly while the oocyte resumes meiosis and extrudes the second polar body. Male and female pronuclei become visible and migrate until they are in close apposition. In that stage, the membranes of the pronuclei disappear, the male and female chromosomes intermingle syngamy is achieved.

Fertilization steps:

- Sperm capacitation.
- Sperm-zona pellucida binding.
- The acrosome reaction.
- Penetration of the zona pellucida.
- Sperm-oocyte binding.
- Egg activation and the cortical reaction.
- The zona reaction.
- Postfertilization events.

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Recently a new biomarker "zinc sparks" was introduced to determine the moment the process of fertilization is completed, the transition of an oocyte to preembryo.

The fertilization of a mammalian egg produces "zinc sparks," caused by the release of the sparks originating from miniature, tiny zinc-rich packages just below the egg's surface.[1]

A stunning explosion of zinc fireworks occurs when a human egg is activated by a sperm enzyme, and the size of these "sparks" is a direct measure of the quality of the egg and its ability to develop into an embryo.

Preembryo development *in vitro*:

- The mean time for the first (two-cell) and second (four-cell) cleavages is 35 and 45 hours postinsemination (day 2).
- The mean time for the third cleavage (eight-cell) is 54 hours postinsemination (day 3).
- Activation of the embryonic genome: utilization of embryonic messenger RNA for protein synthesis.

Morula = compacted embryo, 16–32-cell.

- External cells will give rise to the trophoblast cells.
- Internal cells will become the inner cell mass (ICM).

Blastocyst = day 5–6.

- Cavitation: The trophoblast cells secrete a fluid to create a blastocoel cavity.
- The ICM, which will give rise to the embryo, is clearly distinct from the trophoblast cells which are required for implantation.
- The percentage of two-cell embryos reaching the blastocyst stage is usually (25%).

Fast-cleaving preembryos, with good morphology (no fragments, regular blastomeres) able to reach the blastocysts stage are considered good-quality preembryos with a high implantation potential. This quality depends on the intrinsic characteristics of the preembryos but also on the cultural conditions.

Preembryo Culture Conditions

Preembryo culture conditions are important for the ART outcome and its pre and postimplantation development. The pioneer units of *in vitro* fertilization (IVF) were making their own cultural media.

The culture medium supports the preembryo from the very beginning until the transfer. After the first mitotic divisions, zygotic genome activation, compaction, morula formation, cavitation, and blastocyst formation.[2,3] The development of ART over the past 35 years has led to a huge commercial activity of cultural media. Over the years, basic research on the metabolism of preimplantation embryos revealed that there are specific needs depending on the developmental stage of the embryo. Gardner et al.[4] showed significant differences in the concentrations of various metabolites between the fallopian tube and the uterus cleaving embryos use pyruvate and lactate as energy sources and nonessential amino acids for protein metabolism. From the eight-cell stage, the major energy source is glucose and for protein metabolism the embryos use essential amino acids. Based on their studies they formulate the composition of two culture media G1 and G2. G1 supports the *in vitro* development of the zygote, to the eight-cell stage, and G2 from eight-cells to blastocyst. Sequential media are now being used successfully in IVF treatment all over the world. These lab-controlled environmental variables can affect media efficacy and embryo development, resulting in significantly different outcomes among facilities. Specifically, conditions within the laboratory incubator, such as oxygen tension, pH, and temperature stability, can all significantly impact embryo development.[4]

Composition of the Embryo Culture Medium[5]

Culture media containing a phosphate buffer or HEPES organic buffer are used for procedures that involve handling gametes outside of the incubator, flushing follicles, and micromanipulation.

Most culture media utilize a bicarbonate/carbon dioxide buffer system to keep pH in the range of 7.2–7.4. A humidified incubator with a temperature setting of 37.0–37.5° C should be used for oocyte fertilization and preembryo culture. Preembryos should be cultured under paraffin oil, which prevents evaporation of the medium preserving a constant osmolarity. The medium is composed of 99% water. The purity of the water is crucial[5] and is achieved by ultrafiltration. The medium contains recombinant albumin or synthetic serum. Salt solution of sodium chloride, potassium chloride, calcium chloride, magnesium, and sodium bicarbonate. Carbohydrates together with the amino acids are the main energy source for the preembryo.

Media that support the development of eight-cell embryos up to the blastocyst stage contain pyruvate and lactate in low concentrations and a higher concentration of glucose.Supplement of the culture medium with amino acids is necessary for preembryo development. Media that support the development of zygotes up to eight-cells are supplemented with no essential amino acids while support the development of eight-cell preembryos up to the blastocyst stage are supplemented with essential amino acids. Most media contain vitamins and antibiotics to minimize the risks of microbial growth. Ethylenediamine tetraacetic acid (EDTA) is used as a chelator in a medium that supports the embryo from the zygote stage to eight-cells and prevents abnormal glycolysis.

Preembryo Cryopreservation

Since the first pregnancy and delivery with cryopreserved preembryo were reported (Trounson and Mohr, 1983).[6] Cryopreservation of preembryos is a routine and essential aspect of ART.

Cryopreservation of preembryos decreased the number of fresh embryo transfers, reduced multiple pregnancies, and maximized the effectiveness of IVF. Cryopreservation of preembryos is a crucial approach in cases of canceled embryo transfer due to ovarian hyperstimulation syndrome (OHSS) risk, uterine bleeding, and unsuspected medical conditions of the.[7,8] The proportion of cryopreserved embryo transfer cycles compared with fresh cycles is growing worldwide.

Two freezing technologies are applied worldwide to cryopreserve human preembryo in the cleavage stage, zygote to blastocyst, slow freezing, and vitrification. Slow freezing involves the addition of a cryoprotective agent to prevent the formation of ice crystals in the cells after the cells are cooled gradually under computer control to –196°

C. Vitrification method is rapid cooling of preembryo so fast that ice crystals never form. It has been shown to be superior to slow freezing especially freezing of blastocyst. In the early days of freezing, approximately 20% of embryos did not survive the freezing/thawing process, thought to be due to subtle damage suffered by the embryo during the cooling and/or warming transition. Several factors influence the success rate of freeze-thaw cycles, including the age of the patient at the time of cryopreservation, the cause of infertility, the grade of the embryos being transferred, and the extent of embryo damage after thawing cryopreservation techniques. Present data can ensure maximal frozen embryo viability and minimal risk of cryo-damage**.** Recent studies have found that children born after the transfer of frozen-thawed embryos have better perinatal outcomes than those born after the transfer of fresh embryos—lower rates of preterm birth, low birth weight, growth restriction, perinatal mortality, and malformation rates.[8] In the blastocyst stage, vitrification is more efficient than slow freezing, in terms of postwarming survival rate. Preembryo cryopreservation generated ethical, moral, and legal issues. Some countries have enacted specific laws that restrict preembryo freezing.

Preembryo Assessment: Noninvasive Methods

Morphological scoring of preembryos has been used since the introduction of IVF[9] to define embryo development. An urgent need for a simple and practical method for embryo selection is required in order to maximize the chances of success and minimize the problems of multiple pregnancies in couples treated with assisted reproduction.

Assessment of morphological feathers as a reliable non-invasive method that provides valuable information in the prediction of IVF outcomes has been practiced for 40 years.

Preembryo assessment has many potential benefits such as:

- Accurate selection of embryos prior to transfer.
- Reduction of the risk of multiple pregnancies.
- Assessment of different cultural media.

Morphological noninvasive quality assessments are performed at different stages of preembryo development:

- Cleavage stage embryos (day 3 after insemination).
- Blastocyst stage embryos (day 5 after fertilization).

At the cleavage stage, the different morphological parameters are evaluated:

- Pronuclear scoring systems.
- Cleavage-stage scoring systems.
- Cell number.
- Fragmentation.
- Symmetry.
- Multinucleation.

At the blastocyst stage—the degree of blastocyst expansion as well as the morphological appearance of the ICM and the trophectoderm cells are assessed.[10]

The 4s of ART practice have shown that none of the morphological assessments have a high accuracy to identify the embryos that have good implantation potential. At no point was morphology discriminatory to exclude embryos from transfer.

In recent years[11] it has been shown that preembryos can be selected on the basis of their morphokinetic changes from the time of fertilization until blastocyst formation using time-lapse photography. An automatic system is introduced into the incubator.

Genetic Testing of Preembryo

Preimplantation genetic diagnosis (PGD) application has become possible through the development of artificial reproductive technology and sensitive molecular methods allowing genetic analysis at the single-cell level.

The first clinical application of PGD was described by Handyside et al.[12] The goal of preimplantation testing [preimplantation genetic screening (PGS)/PGD] is to reduce the likelihood of conceiving a child with severe disease or to reduce miscarriages. It may also increase the chance of pregnancy in the case of couples with advanced maternal age, recurrent pregnancy loss, or repeated IVF failures.[13] PGD followed by implantation of unaffected embryos offers high-risk couples the option to decrease the risk of genetic disease in their offspring without the dilemma of a prenatal diagnosis that may be followed by a termination of pregnancy. There are several techniques to sample DNA at this early stage without having an impact on the viability of the conceptus. These include biopsy of the first and second polar bodies when a mutation is maternally inherited, aspiration of one or two cells from six to eight-cell embryo at 2–3 days postconception (blastomere biopsy), and, although rarely performed, biopsy of the trophectoderm taken from an embryo at the blastocyst stage. The genetic analysis involves DNA amplification using a variety of strategies (whole-genome amplification, polymerase chain reaction amplification), followed by the use of one of several available platforms for analysis of the amplified DNA.[14] At present a new terminology of genetic evaluation of preembryo was introduced—preimplantation genetic testing (PGT) which includes the following categories.[15]

Preimplantation Genetic Testing for Aneuploidy (PGT-A)

The PGT-A is to identify embryos with *de novo* aneuploidy, including subchromosomal deletion and additions in preembryos of a couple presumed to be chromosomally normal. PGT-A also known as PGS is a genetic test that allows the determination of the chromosomal status of IVF embryos by screening all 23 pairs of human chromosomes. Only embryos with the correct number of chromosomes will be able to develop into a healthy baby. PGT-A test is able to identify those embryos free from chromosome abnormalities (euploid embryos) that are more likely to implant and result in a healthy live birth. By selecting healthy embryos with the

right number of chromosomes to be transferred to the uterus, PGT-A is genetic testing for aneuploidy, which improves IVF success, increasing the likelihood of pregnancy per transfer.

- Reduces the risk of miscarriage.
- Allows for confident single embryo transfer, reducing the risks and complications associated with multiple pregnancies.
- Reduces time to pregnancy by allowing the identification of a normal embryo as soon as possible.
- Avoids the live birth of a baby with genetic disorders.

Preimplantation Genetic Testing for Monogenic (PGT-M) (Single-gene) Disorders

The PGT-M testing is to establish a pregnancy that is unaffected by specific genetic characteristics, such as a known heritable genetic mutation carried by one or both biological parents. It is also used to select embryos for transfer that have specific characteristics, such as a particular gender or compatible human leukocyte antigen complex type. PGT-M diseases for adult-onset conditions are ethically permissible for a range of conditions including when the condition is serious and no safe, effective interventions are available.

Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR)

The PGT-SR is to establish a pregnancy that is unaffected by a structural chromosomal abnormality (translocation) in a couple with a balanced translocation or deletion/duplication. New technology may actually distinguish normal noncarrier embryos from balanced carriers. In PGT, a biopsy is necessary for obtaining embryonic material for genetic analysis. PGT requires an invasive biopsy to obtain embryonic material for genetic analysis. PGT may result in damage to the preembryo or may lower the implantation potential of the preembryo. This is less likely if the preembryo biopsied is at the blastocyst stage. Recent studies demonstrated that aspiration of blastocyst fluid is a promising alternative source of DNA for PGT.

Legal Status of the Preimplanted Preembryo[16–18]

The legal status of the preembryo is difficult to establish if it is regarded as a person or even a potential person. It has no legal status according to the law in most countries. There is a suggestion that the preembryo is property. However, this definition offends ethical principles. The above suggestions leave open the legal question of the right to use, dispose of sell, and purchase a preembryo. A preembryo seems not to be a human being for the purposes of criminal law. Deliberate destruction of a preembryo is not a criminal "abortion" act. The legislation regarding the storage of preembryos in Australia, United Kingdom and regulations in other countries give the gamete donors the right to decide their fate. According to the wishes and consent of the gamete donors it can be disposed of, donated to other couples, or given for research (this differs from country to country). Present consensus on the status of the preembryo has been documented by several ethical committees. United States of America Advisory Board states that the preembryo is entitled to profound respect, but this does not necessarily give him the full legal and moral rights attributed to persons. The Warnock Committee—the human embryo is not, under the present law of the United Kingdom, accorded the same status as the living child or an adult.

The proposed Federal Human Life Bill in the United States of America would not give all the legal rights of personhood to the preembryo from the moment of conception. This is not similar in all states. The legislation in Illinois (United States of America), applied to the preembryos legal status *in vitro,* is that of the 1877 Child Abuse Act. The physician is criminally liable if he endangers the life or health of the preembryo. This may lead to the situation whereby physicians can be prosecuted when the IVF preembryo is damaged during its growth in *vitro* by changing the growth medium, or temperature or following the use of manipulation techniques. A further question arises as to whether the physician commits a crime if he discards a preembryo that is not dividing properly or is damaged by the procedure of IVF or its storage. There is a general consensus that the preimplanted preembryo is not a person but should have its own legal rights and should be treated with special respect since it may become a person. Therefore, any intervention with the preembryo that is subsequently transferred to the uterus creates obligations not only to avoid hurting or injuring it but even to apply therapeutic measures since, following transfer, it may be born. This viewpoint imposes the traditional duty of reasonable prenatal care and raises the question that if therapy is not undertaken, can the physicians and the parents, the donors of the gametes, be sued for wrongful life? The basis for this assumption may be a decision by the Supreme Court of the State of Israel on the issue of wrongful life. The Israeli Supreme Court of Appeals decided that it has the power to deal with the matter of the right not to be born and decided that the minor has a valid claim against the physician. Therefore, the physician has a duty to care for the unborn. Damages were assessed against the physician for wrongful life so, according to this decision, it seems that the minor has the right to sue his negligent parents if antenatal care, even at the preembryo stage, is not undertaken.

Moral Status of Preembryo[19–21]

The central question regarding therapeutic approaches to the preimplantation preembryo is its moral status. There are three options for the definition of the moral status of the preembryo:

- The preembryo has no moral status—it is a collection of undifferentiated cells lacking individuality and therefore has a status that is no different from that of any other human tissue. The consequence of this assumption is that we have no obligation to treat the preembryo.
- The preembryo has the full status of a human being. The basis for this assumption are—(1) a new genotype is established during fertilization; (2)some of the preembryos

have the potential to become full-term fetuses, children, and adults. The consequences of this assumption are that the preembryo has its own rights, the gamete donors are the guardians of the preembryo and the interests of the mother are irrelevant to the future of the preembryo. Therefore, society has an obligation to apply therapeutic measures to the preembryo.
- The preembryo is a potential human being. This definition is a new philosophical entity, representing a compromise between the other two, and is the one accepted today by most of the scientists, physicians, and ethicists. Even though the preembryo is a potential human being, it should be handled with dignity and its rights should be respected as long as they do not harm major social, maternal, or other interests.

For some purposes life is started to begin at implantation The regulations regarding federally funded research in the United States of America with pregnant women or with fetuses define pregnancy and fetal life as beginning with implantation. Life has been defined as ending when brain activity ceases. Therefore, some consider that life begins when brain activity starts. The beginning of life is 8 weeks after conception at the point when the embryo is responsive to stimuli.

Human life begins when the human conceptus becomes a person, has some degree of sentience, or even an active volition. According to the above statements, apart from the one supported by the Catholic Church that human life begins at conception, human life cannot be attributed to the preembryo in the *in vitro* status. Therefore, the question arises whether the gamete donors and the medical staff have an obligation to apply medical measures.

Human Genome Editing

Genome editing is a technology able to change the DNA of a cell or organism by adding or removing DNA in the genome. The technology uses specific enzyme nucleases which cuts the genome in a specific place. The specific nucleases are made up of two parts:

- Nuclease part that cuts the DNA.
- The DNA-targeting part is designed to guide the nuclease to a specific sequence of DNA.

After cutting the DNA in a specific place, the cell will naturally repair the cut DNA. It is possible to manipulate the repair process, to make changes to the DNA in that location in the genome.[22] There are two different categories of gene therapies:

- Germline therapy.
- Somatic therapy.

Genome editing of human somatic cells aims to repair or eliminate a mutation that could cause diseases like cancer patients.

Clinical experiments demonstrated positive results. It was approved to modify human blood cells to treat conditions including patients with malignancy and acquired immunodeficiency syndrome (AIDS). Changes to the DNA of somatic cells affect only the person who receives the gene therapy.

Germline therapies change DNA in reproductive cells (sperm, oocyte, and preembryo) and are passed down from generation to generation. Genome editing of preembryo has the potential to cure and eradicate genetic diseases. On the contrary, deliberately changing the genes passed on to children and future generations creates genetically modified people. Chinese scientists led by Huang[23] have reported editing the genomes of human embryos. The team was using "nonviable" embryos, which cannot result in a live birth, because were obtained from local fertility clinics. The team attempted to modify the gene responsible for β-thalassaemia, a potentially fatal blood disorder, using a gene-editing technique known as CRISPR/Cas9. Huang et al. set out to see if the procedure could replace a gene in a single-cell fertilized human embryo; in principle, all cells produced as the embryo developed would then have the repaired gene. The results revealed that only part of the cells was successfully spliced and that only a fraction of those contained the replacement genetic material His team also found a high rate of mutations assumed to be introduced by the CRISPR/Cas9 complex acting on other parts of the genome. This effect is one of the main safety concerns surrounding germline gene editing because these unintended mutations could be harmful. Genome editing of preembryos at present has not proved to be safe. Questions are raised by society regarding—social, legal, ethical, religious, and economic implications of the technique. At present ethical committees[24] support research aimed at making gene editing safe in order to medically treat existing people, but urge a prohibition on its use to create genetically modified humans.

Mitochondria Manipulation: A Three-parent Babies

Mitochondria are located in the cytoplasm of cells along with other organelles of the cell. Preembryo possesses a nucleus that contains a genome comprising nuclear DNA from both the father and the mother and mitochondria that house a distinct genome, which is solely composed of mitochondrial DNA (mtDNA). Maternally inherited mtDNA accounts for only a very small percentage of the total DNA in cells, <1%. Mutations in mtDNA are a cause of mitochondrial disease. Correlations have been identified between reduced mtDNA quantity and infertility, as well as between mtDNA mutations and fertilization rates. Mitochondrial genetic disorders can be caused by the mtDNA or nuclear DNA that leads to dysfunction of the mitochondria and inadequate production of energy. Those caused by mutations in mitochondrial DNA are transmitted by maternal inheritance.

There are a few methods of transferring mitochondria:

- Pronuclear transfer.
- Spindle transfer.

In pronuclear transfer, both the maternal oocytes and the donor one are fertilized *via* IVF. The fertilized pronucleus of the donor oocyte is destroyed and replaced with the fertilized nucleus of the maternal oocyte which has the DNA of the mother and the father. In spindle transfer, the nuclear DNA from the mother (known as a spindle) is transplanted into the donor's oocyte replacing the donor's DNA. This new oocyte is fertilized by the father's sperm *via* intracytoplasmic sperm injection. Defective mitochondria of the woman's oocyte are replaced with mitochondria from a donor who did not carry the mutation. IVF is performed and the resulting child carries DNA from three people—the female nuclear DNA donor (mother), the male nuclear DNA (father) or sperm donor, and the female mitochondria donor (additional mother). The first baby born using mitochondrial replacement therapy was a Jordanian couple by Zhang et al.[24] The mother of the baby boy is a carrier of Leigh disease, a rare neurometabolic disorder that decimates a child's muscular system and often results in respiratory failure and death. The three-parent babies will still resemble the men and women whose sperm and oocyte combined to produce the 23 chromosomes in the nucleus of that first cell. At present the technology of mitochondria manipulation is forbidden in the United States of America but permitted in the United Kingdom.[25]

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