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Ethical Treatment of Human Embryos

"It is in Man's power to treat himself as a mere 'natural object' and his own judgments of value as raw material for scientific manipulation to alter at will. The objection to his doing so does not lie in the fact that this point of view (like one's first day in a dissecting room) is painful and shocking till we grow used to it. The pain and the shock are at most a warning and a symptom. The real objection is that if man chooses to treat himself as raw material, raw material he will be: not raw material to be manipulated, as he fondly imagined, by himself, but by mere appetite, that is, mere Nature, in the person of his dehumanized Conditioners." – C.S. Lewis[1]

Background

Each of us begin our existence as a human embryo, and from our embryonic beginnings, we experience continuous development and differentiation throughout life.[2] As medical professionals who live out the Hippocratic Oath,[3] we have a compelling responsibility to the human beings under out care. As medical professionals in obstetrics and gynecology, we have a long history of recognizing that both the pregnant mother and the human being in her womb are our patients. "Through quality perinatal care, the specialty promotes the health and well-being of the pregnant woman and her fetus."[4] We have the privilege and responsibility to care for both of them.

Our responsibility to care for our youngest patients begins when a new human organism begins. Thus, the key scientific question addressed by this Committee Opinion is whether or not the embryo is a human organism, i.e., a human being. The answer to this question has significant implications for the practice of Assisted Reproductive Technology (ART), especially In-Vitro Fertilization (IVF), and also fore the creation and use of human embryos for research, as exemplified by the recent proposal introduced in the UK Parliament for the creation of human embryos in "industrial quantities" for experimentation.[5] This Committee Opinion will explore the scientific evidence surrounding the beginning of a human organism/human being and then the necessary implications of this information for the ethical treatment of embryos in both research and IVF.

AAPLOG Committee Opinion. This document was developed by 4 authors on the Research Committee. Committee Opinions summarize best practices that form an important part of pro-life practice.

What kind of entity is the human embryo in vivo?

Embryos in vivo start as the product of sperm-egg membrane fusion in the mother's fallopian tube. Sperm-egg membrane fusion results in the creation of a zygote, which is a one-celled embryo. Dr. Maureen Condic has published the key scientific considerations that bear on the specific question of the kind of entity produced by sperm-egg membrane fusion. The two key questions that must be considered are 1) When is a new cell formed that is distinct from the sperm or the egg? and 2) Is the resulting new cell a human organism (i.e., a new human being)? Condic answers these questions as follows:

> Based on universally accepted scientific criteria, a new cell, the human zygote, comes into existence at the moment of sperm-egg fusion, an event that occurs in less than a second. Upon formation, the zygote immediately initiates a complex sequence of events that establish the molecular conditions required for continued embryonic development. The behavior of the zygote is radically unlike that of either sperm or egg separately and is characteristic of a human organism. Thus, the scientific evidence supports the conclusion that a zygote is a human organism and that the life of a new human being commences at a scientifically well defined "moment of conception." This conclusion is objective, consistent with the factual evidence, and independent of any specific ethical, moral, political, or religious view of human life or of human embryos.[2]

Elsewhere, Condic states:

> . . . the embryo acts in a coordinated, organismal manner to produce and to regulate its own development. All of the actions of the embryo are directed toward producing the structures and relationships required for the ongoing life and health of the embryo as a whole. At no time does the embryo even remotely resemble a mere human cell or collection of human cells.[6]

It is clear that the defining feature of an embryo is organized self-directed growth and development, which begins at the moment of sperm-egg membrane fusion. The zygote clearly exhibits subsequent changes in the metabolic activity and actions that mark the zygote as a human organism, distinct from either the oocyte or sperm. He or she is an organism at the zygote state. This human being has one continuous biological existence throughout his or her developmental states, from zygote through the states of embryo, fetus, newborn, toddler, child, teen, adult, and aged adult, until the life of that human being ends in death. Human beings have different lifespans, some spanning decades, some spanning years or days, and some spanning seconds or minutes in the embryonic state. The age of a human being is not determinative of his or her value.

Sperm-egg fusion in vivo does not always result in an embryo.

Although some products of sperm-egg fusion may be embryos with a life-limiting condition and some gametes may be deficient in ways that prevent an embryo from forming upon the fusion of the sperm and egg membranes, sperm-egg membrane fusion is clearly the point at which human life in vivo naturally begins. Again, while nutrients are required, this new organism is self-integrated and oriented toward its own survival. The same is true for every other species that begins with a fusion of male and female gametes.

Deficiencies in either sperm or egg may result in an inability to form an organism at sperm-egg fusion. One example in vivo is the case of a complete hydatidiform mole (CHM). CHM forms when only paternal DNA is present to bind to an egg devoid of a nucleus. "In complete moles, the karyotype is 46XX 90% of the time and 46XY 10% of the time. It arises when an enucleated egg is fertilized either by two sperms or by a haploid sperm that then duplicates and therefore, only paternal DNA is expressed."[7] The CHM does not have organized self-directed growth and universally forms a disorganized tumor. Therefore, the CHM is not an embryo.

At this time, we do not have the ability to detect other examples of sperm-egg membrane fusion in vivo that do not meet the criteria of an organism. Detection of such entities would require a marker to detect sperm-egg membrane fusion in vivo, which currently is unknown. We also do not know the rate of in vivo formation of embryos with life-limiting conditions that do not continue to implantation. To determine the rate of in vivo formation of embryos with a life-limiting condition will require the development of a fertilization marker and application of this marker to normal sexually active females in the late luteal phase, compared to the subsequent pregnancy rate in that population.

Sperm-egg fusion in vitro does not always result in an embryo.

In vitro fertilization allows for the direct observation of the initial states of embryo development, albeit in an environment that does not entirely mimic the conditions in vivo, which may affect the results observed.

Estimates based on recent data show that during IVF cycles, approximately 70-79% of oocytes exposed to sperm form normal zygotes (the fertilization rate, as evidenced by the formation of two pronuclei, i.e., "2PN embryos" as shown in Figure 1, Day 1), while some older data show a fertilization rate of 53-81%.[8,9]

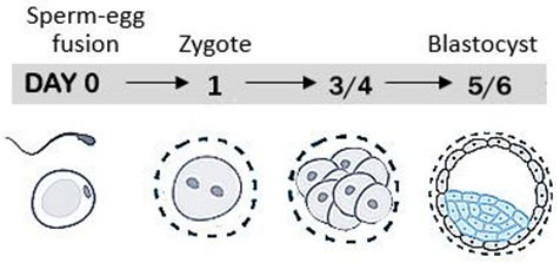

Figure 1 – Day 0 to Day 6

AAPLOG affirms the objective biological fact states earlier that the product of

sperm-egg membrane fusion is a human embryo in the zygote state of human life:

> [T]he scientific evidence supports the conclusion that a zygote is a human organism and that the life of a new human being commences at a scientifically well defined "moment of conception." This conclusion is objective, consistent with the factual evidence, and independent of any specific ethical, moral, political, or religious view of human life or of human embryos.[2]

We recognize that roughly a third of these embryos formed in vitro will have life-limiting conditions where the zygote initiates development, but development arrests. According to Romanski et al., of the entities formed at sperm-egg membrane fusion (zygote) in vitro, approximately one-third will not continue development to the point of blastocyst formation.[10] However, a short duration of embryo survival does not mean that the embryo did not exist, just a short duration of human life at any state does not mean that a human being did not exist.

Some pro-life medical professionals hold an alternative view that after sperm-egg membrane fusion, the entity formed must demonstrate continued organized development to be recognized as a human being. This view would state that some of the products of sperm-egg membrane fusion are non-embryos and that an embryo cannot be definitively distinguished from a non-embryo until that non-embryo ceases to exhibit continued organized growth toward the functioning of the organism as a whole.

In this alternative view, it is recognized that we have no means of distinguishing non-embryos from embryos at the zygote stage and no means at that stage of distinguishing non-embryos from embryos with a life-limiting genetic, epigenetic, or physiological limitation that does not allow for continued embryo survival.

When there is uncertainty as to whether or not a human embryo has been formed, we ought to err on the side of caution. This ethical principle is routinely applied in other situations where innocent human life may be at risk, such as hunting. For example, if deer hunters see movement in the bushes, they are compelled not to shoot until they determine definitively that the movement is from a deer, not a human.

With either viewpoint, we are compelled to treat all of the products of sperm-egg membrane fusion as human embryos until it becomes clear that they are not continuing to exist as living embryos, either through lack of development, cessation of development, or chaotic development.

From either viewpoint, however, we can say with certainty that when a human-derived organism shows development consistent with the corresponding stage of human embryonic life, then that entity meets the criteria for being a human embryo, even if that embryo cannot continue development due to genetic, epigenetic, or physiological limitations.

Embryos can be formed in vitro by means other than sperm-egg fusion.

In vivo (under natural conditions), sperm-egg fusion is the point of initiation of the human zygote, a new human being. However, in vitro, an embryo can also be formed by other mechanisms, which result in an entity with the structure and function of a normal embryo at an equivalent stage of development, as exemplified by human embryo models made from stem cells, which will be discussed below. In this case, in which there is no sperm-egg fusion, it is the continued organized function of the human organism toward the well-being of the human organism that confirms what is and is not a human embryo.

Ethical Treatment of Human Embryos in Research

Research with embryonic stem cells has produced a variety of entities, including human embryos, by means which bypass sperm-egg fusion. Some of those entities are human embryos because they fulfill the criteria of a human organism: *"The critical difference between a collection of cells and a living organism is the ability of an organism to act in a coordinated manner for the continued health and maintenance of the body as a whole."*[11] When a human-derived entity exhibits the ability of an organism to act in a coordinated manner for the continued health and maintenance of the body as a whole, that entity is a human organism, i.e., a human being.

What, the, are the responsibilities of the scientific and medical communities toward respecting the human rights of these vulnerable human beings in research?

The ethical responsibilities of human subject researchers are drawn from and mirror the ethical responsibilities of medical professionals toward their patients. There are three international consensus documents addressing the ethical responsibilities of medical professionals and researchers toward human subjects:

A. The Hippocratic Oath, which formed the basis of medical ethics,

B. The Helsinki Declaration of the World Medical Association, and

C. The Belmont Report, which was formulated in the U.S. after the atrocities committed by the scientific and medical communities in WWII.

We briefly examine the pertinent principles here:

A. The Hippocratic Oath

The Hippocratic Oath states, "I will always seek the physical and emotional well-being of my patients, according to my best ability and judgment, being careful to cause no intentional harm."

In recognition of our shared humanity, the Hippocratic Oath calls both medical professionals and human subject researchers to hold the well-being of the human subject paramount. In research, this means not conducting experiments on human subjects, including human embryos, which could possibly lead to their

death or harm. It also means assigning proxy decision-makers charged with defending the life and well-being of vulnerable human beings in cases where informed consent from the subject cannot take place.

B. The Helsinki Declaration of the World Medical Association[12]

The following are excerpts from the Helsinki Declaration which discuss medical research on human subjects [numbers in brackets represent the page of the Helsinki Declaration where the quote is found]:

> The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. [1]
>
> Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles. [2]
>
> While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects. [8]
>
> It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. [9]
>
> Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects. [16]
>
> Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. [18]

The Helsinki Document also directly addresses research involving vulnerable groups and individuals:

> Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection. [19]
>
> Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices, or interventions that result from the research. [20]
>
> For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote

the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden. [28].

C. The Belmont Report[13] (National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research)

The Belmont Report also discusses medical research on human subjects:

> Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.
>
> 1. Respect for Persons. – Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy. . . Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated. Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them;. . . The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit.
> 2. Beneficence. – Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. . . Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms. The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others.
> 3. Justice. – Who ought to receive the benefits of research and bear its burdens? . . . the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population.
>
> The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assess-

> ment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.
>
> Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all.[13]

All three of these international consensus documents recognize the vulnerability of some human populations to exploitation and harm. Some vulnerable populations cannot advocate for or defend themselves against exploitation. Human embryos constitute one of those vulnerable populations. To date, the scientific and legal communities have not exercised responsible limitations to prevent exploitation and harm to human embryos in research. Instead, the scientific community has generally ignored the intrinsic ethical problem produced by research using embryonic human beings. Legally, human embryos are considered property.

The gruesome proposal to create human beings solely for the purpose of experimentation (Human Embryonic Models, a.k.a. HEMs)

Worldwide, most communities of researchers recoil at the creation of human beings solely for the utility and benefit of other human beings. Yet this is precisely the kind of research currently underway worldwide.[14,15] It is a particularly gruesome concept to create vulnerable human beings for the explicit purpose of experimentation. Even worse is the creation of human beings for the purpose of deforming them to study human deformities. It violates the principles of respect for persons as well as beneficence and justice outline in the Hippocratic Oath, the Declaration of Helsinki, and the Belmont Report, all of which still serve as the basis for research ethics in the United States. A recent article in the lay press gives an example of an attempt to normalize the creation of embryonic human beings for experimentation in order to induce the general public to accept the concept:

> Scientists in Cambridge have created synthetic mouse embryos in a lab, without using eggs or sperm, which show evidence of a brain and beating heart. . .. Eventually, their ambition is to develop similar embryos from human stem cells – but this is still a long

way off, and ethically much more complicated.

At present, UK law permits human embryos to be studied in the laboratory only up to the fourteenth day of development, but there are no rules around synthetic embryos.

Prof. Robin Lovell-Badge, from the Francis Crick Institute, said that should change.

"Given the similarity with real embryos, it follows that consideration also needs to be given as to whether and how such integrated stem cell-based embryo models should be regulated," he said.

He added that it was important not to think of the embryo-like models "as being the real thing – even if they are getting close."[16]

The obvious problem is that, in fact, these "embryo models" are "the real thing." An entity with human DNA that has organized development through organogenesis meets the criteria for being a human embryo, i.e., a human being, even if that human being does not continue through subsequent development to birth. As previously noted in Condic's work, the ability of an organism to act in a coordinated manner towards the health and well-being of the organism as a whole is what characterizes that entity as a living organism.[11]

There is currently a proposal in the UK to eliminate the rule that human embryo experimentation must be stopped at 14 days post-fertilization, the so-called "14-day rule." The Code of Practice for the Generation and Use of Human Stem Cell-based Embryo Models was recently submitted to the UK Parliament for ratification in early 2025.[5] The reasons given for the relaxation of that rule are nothing short of horrific: allowing the creation of embryonic human beings called "Human Embryo Models" (HEMs) for the purposes of exposing these human beings to toxic drugs in order to study the resulting deformation and to use these human beings as subjects of drug experimentation. To quote from the Parliamentary Office of Science and Technology (POST) Report:[17]

[Note: references here are renumbered from the original POST Report and are cited below for availability in the end notes of this Committee Opinion.]

HEMs can be generated from either of these stem cell types (hESCs or hiPSCs) using various methods.[18] These methods include controlling the space in which the cells grow, altering the nutrients supplied, and/or by genetically manipulating the cells.[15,19,20]

Classification of HEMs

Guidelines drawn up in 2021 by the International Society for Stem Cell Research (ISSCR) classify HEMs into integrated and non-integrated classes. It also suggests that each be subject to different levels of regulations (see section Amendment of ISSCR guidelines (2021)).[29]

Non-integrated HEMs

Non-integrated HEMs only partially mimic the developing embryo. They

do not include certain cell types (extra-embryonic cells) that are crucial to the development of the embryo. Therefore it is thought they lack the potential to develop into a fetus.[30-32] Non-integrated HEMs may include:

- 2D micropatterns, where stem cells are grown in a controlled space to trigger their self-organisation properties of early development,[19]
- gastruloids, which have features of a developmental stage of the embryo called gastrulation when the body outline forms (see Figure 1),[33-35]
- models of the fluid-filled sac, called the amniotic sac, within which the embryo develops inside the body,[36,37]
- or early features of the developing nervous system (called neural tubes).[36]

Integrated HEMs

Integrated HEMs mimic the development of the entire embryo and contain both embryonic and extra-embryonic cell types. They are thought to have the potential to develop into a fetus.[38] Integrated HEMs can include:

- blastoids, that represent a developmental stage of the embryo called the blastocyst which occurs 5-7 days after fertilization (see Figure 1),[39-43]
- models that represent human embryos up to 14 days after fertilization[15,20]

What is being described and requested in the UK via POST Report is no less than allowance for the creation of human beings for the explicit purpose of experimenting on those human beings. The POST Report describes the creation of human beings in order to expose those human beings to teratogens and to mass produce those human beings for pharmaceutical experimentation. This is a gross violation of the international consensus statements protecting the rights of human subjects in research.

Outlined below are the research agendas proposed in the POST report:

> **Potential applications of HEMs**
>
> . . . Scientists argue that HEMs provide a sustainable way to supplement the supply of embryos that researchers need.[44] HEMs are seen as a key advance for understanding embryo development, for research progress and in developing clinical treatments.[45]
>
> **Early pregnancy loss and IVF outcomes**
>
> The use of HEMs to study early embryonic development is relevant to conception naturally or via IVF. Approximately 50% of fertilised human eggs fail to develop during IVF treatment.[40,46-48] Even after successful conception, 1 in 5 pregnancies are reported to end in miscarriages (CDP-2021-0128), and pregnancy-related

conditions, such as pre-eclampsia, cause over 50,000 maternal and 500,000 fetal deaths worldwide (PN 527).[49-51] HEMs can provide detailed scientific data on biological mechanisms of early embryo development and this information can be used to improve IVF treatment outcomes and reduce risks of early pregnancy loss.[52]

Disease modelling

In 2019 in the UK, approximately 1 in 46 births were diagnosed with congenital abnormalities.[53] HEMs can be used to investigate the origins of congenital abnormalities. HEMs can reflect the complexity of conditions within a living organism and be developed to a particular stage that is most relevant for the disease.[54]

Researchers are generating HEMs to investigate various conditions such as:

- malformations of the fetus' spine,[55]
- the impact of disrupting key signals involved in the early development of the nervous system,[56]
- neurodegenerative diseases such as Huntington's,[56]
- and early heart development which could help understand congenital heart disease (CHD),[57] one of the leading causes of death in new-borns.[58]

In cases of rare diseases (CDP-2017-0105) where there are limited samples for research, HEMs offer the opportunity to model diseases from the patients' iPSCs.[59]

Toxicity studies of the developing human embryo

While most studies of teratogens (chemicals that cause harm to the growing embryo or fetus) are conducted on model organisms, such as mice, they do not capture species-specific responses.[60] For example, researchers have used HEMs to test Thalidomide, a morning-sickness drug that resulted in severe birth defects in humans. They found a stronger effect on HEMs compared to mouse embryo models.[61,62]

Large-scale drug discovery

In contrast to human embryos, HEMs can be produced in larger numbers to test multiple compounds for medicinal effects at the same time.[52,63-66]

Source of cell therapy

HEMs are a potential way to generate materials for cell therapy (PN 567, PN 221) where cells are given to a patient for treatment (e.g., CAR T-cell therapy in cancer (PN 598)) or regenerative purposes (PN 620).[67-72]

None of the results of this proposed research will benefit the human beings who are the subjects of these experiments. It is clear that human embryonic models meet the criteria for human beings, although they are derived from stem cells. There is no legal advocate for these human beings created for abuse and exploitation. There needs to be a worldwide outcry against

this premeditated horrific abuse of vulnerable human beings.

Ethical Treatment of Human Embryos in Assisted Reproductive Technology (ART) Practice

The ethical treatment of human embryos in the IVF industry also calls for limitations on what can and cannot be done with created embryos. AAPLOG recognizes that there are pro-life medical professionals of good conscience who reject IVF entirely because of its in vitro manipulation of young human life. Some are also concerned about laboratory experimentation with nascent human beings.

Other pro-life medical professionals of good conscience could potentially accept a form of IVF that is life-sparing but are nonetheless opposed to the often life-destroying practices of the current IVF industry. As a profession that has pledged to protect all of our patients, including the most vulnerable, we must take a serious look at the facts about IVF.

IVF does not treat the underlying pathology that leads to infertility; it provides a technical workaround in hopes of producing a baby. Current IVF practice is often not life-affirming and never life-sparing. Current estimates for the number of embryos that do not survive or are destroyed, discarded, or frozen for storage under usual IVF practices range from 90-98%. Ghazal et al. wrote that the rate of embryo loss in the U.S. is 76.5% but pointedly did not take into account embryos discarded or cryopreserved; these additional embryo losses would give a rate of at least 90%.[73] Likewise, Kovalevsky and Patrizio calculate wastage of embryos as 85% but do not include the number of embryos discarded or lost during thawing from cryopreservation, stating that their 85% rate of loss "greatly underestimates the overall loss."[74] Adjustments for these additional losses would raise the rate of loss over 90%. Gleicher et al. note regarding genetic testing that "Because of the high false-positivity rate, a large number of perfectly normal embryos are now routinely discarded which, if transferred, in surprisingly high percentages still would result in normal births."[75]

Moreover, IVF can pose distinct risks both to mothers and to babies. Before any attempts at IVF, there should be counseling to provide complete informed consent regarding the facts of IVF, including efficiencies, risks, and ethical considerations. Also, before attempting IVF, every effort should be made to diagnose, treat, and resolve the underlying causes of infertility.[76,77] Restorative reproductive medicine has been documented to improve fertility rates even after IVF failure.[78,79] Accurate diagnosis and targeted treatment of the underlying causes of infertility address the real needs of patients and can improve long-term health well beyond pregnancy.

However, if IVF is to be used, it should conform to the respect of human persons inherent in the Hippocratic Oath and also reflected in the 2016 international consensus document, *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice*

(GCP) on the treatment of human subjects which states that "the rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society."[80]

It should be recognized that IVF results in an increased risk to both the mother and the fetus. According to the Society for Maternal-Fetal Medicine, IVF is associated with increased risk for several adverse maternal and perinatal outcomes, including monozygotic twins (even with single embryo transfer), multifetal pregnancy, placental implantation disorders, hypertensive disorders of pregnancy, and stillbirth. Singleton pregnancies conceived by IVF also have a higher risk of preterm birth and small for gestational age infants. Additionally, pregnancies conceived with ICSI have a higher rate of de novo chromosomal abnormalities.

Brief review of the process of IVF

1. Ovarian Stimulation and Egg Retrieval

The process of IVF beings with the collection of eggs and sperm. The collection of eggs most often involves hormonal stimulation to synchronize egg maturation. High-dose hormonal stimulation of the ovaries is done to produce multiple eggs at one time rather than the single egg usually matured per cycle. The eggs are harvested trans-vaginally under ultrasound guidance and then either frozen or fertilized.

2. Fertilization

At this stage, the procedure varies depending on where and how fertilization occurs.

In traditional IVF, which accounts for 99% of procedures, fertilization occurs in vitro. The developmental stages that normally would have occurred in the fallopian tube during transfer to the uterus occur instead in culture media in the petri dish for 3-5 days. Embryos that survive for 3-5 days are candidates for transfer to a uterus.

In Gamete Intra-Fallopian Transfer (GIFT), the eggs and sperm are both transferred to the fallopian tube, which is the normal site of fertilization. Thus, GIFT attempts to utilize the natural environment for fertilization and the first days of human development.

Zygote Intra-Fallopian Transfer (ZIFT) combines egg and sperm in a petri dish for fertilization, as is done with traditional IVF. However, the zygote formed is transferred on day 1 to the fallopian tube, approximating the site and environment where the zygote would have been produced in vivo. This method also attempts to utilize the natural environment for early embryo development.

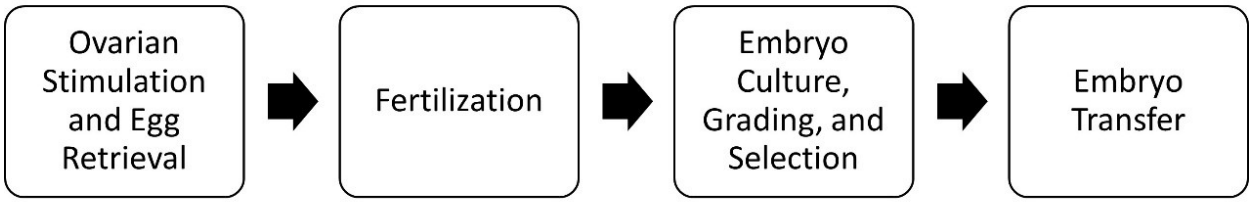

Figure 2 – IVF Process

Intra-cytoplasmic Sperm Injection (ICSI) is a variation of IVF used for sperm-related fertilization failures. The lab technician injects one sperm into each egg under a microscope. After further growth in the lab dish, the embryo is transferred to the uterus as in traditional IVF. There is some increased concern with this procedure since more parts of the sperm enter the egg than in natural in vivo fertilization, and also the significant manipulation of the egg involved.[82-85]

3. Embryo Culture, Grading, and Selection

For GIFT and ZIFT, there is no culturing or grading, as the early days of embryo development take place in the normal in-vivo environment.

In traditional IVF, however, embryos are evaluated and graded. Some embryos do not survive and grow but instead perish in the dish. Embryos that survive 2-5 days' culture are evaluated by various methods and are "graded" by subjective microscope inspection to indicate a judgment of their potential for implantation and development.[86,87] Recently, there has been a movement to incorporate Artificial Intelligence (AI) into the grading of embryo quality.[88] Theoretically, those judged as "high-quality" embryos have a better chance of implantation and gestation to birth, which is the endpoint for grading. However, studies show that even so-called "low-quality" embryos can develop into normal babies.[89] Grading criteria are based solely on the predicted likelihood of subsequent implantation and gestation to birth, not on whether or not the embryo is, in fact, a living human being.

Genetic testing is also used to evaluate embryo quality and specifically to select for or against embryos with various genetic traits. Preimplantation genetic testing (PGT, sometimes termed PGD for preimplantation genetic diagnosis or PGS for preimplantation genetic screening) involves making a hole in the zona pellucida, extracting about five cells from the blastocyst, and then freezing the embryo while the genetic analysis is conducted.[90] The cell(s) undergoes genetic analysis for "fitness." Screening may be for aneuploidies (different chromosome numbers, e.g., trisomies such as Down syndrome) or for specific genetic compositions and traits, including for sex selection and even potential adult-onset disorders (e.g. breast cancer or Huntington's disease). While some early studies showed increased success at live birth using genetic selection of the desired embryos, other recent studies have found the opposite. One recent study found

a significantly lower rate of pregnancies in the women who underwent genetic screening, however. Only 25% achieved ongoing pregnancies, compared with 37% of women who were not screened (rate ratio 0.69, 95% confidence interval 0.51 to 0.93).

The women randomised to preimplantation genetic screening also had a significantly lower rate of live births, at 24% compared with 35% in women who were not screened (0.68, 0.50 to 0.92).[91]

Several studies indicate that PGT lowers the live birth rate;[91] does not improve pregnancy, implantation, or live birth rates;[92] and should not be used except perhaps for research studies.[93] Despite these findings, PGT has become routine as part of IVF. As with visual grading, some embryos labeled "low quality" or "abnormal" by PGT produce healthy babies.[94,95] As one might expect, not all embryos survive having some of their cells removed.

Clinics may offer PGT or other "add-ons" as incentives, claiming they improve the efficiency and survival of embryos to live births. IVF clinics are rated by patients as well as insurance companies based partly on their pregnancy and live birth rates, leading to significant pressure on the clinic to do anything they can to improve the rate of these outcomes. This is a conflict of interest in ethical decision-making. A Cochrane special report noted that "none of the IVF add-ons are supported by high-quality evidence that the add-on is effective and safe."[96]

4. Embryo Transfer

If embryos survive culture, they can be transferred to the endometrial cavity. The number of embryos and their age in days when transferred are important considerations for subsequent gestation. In the past, anywhere from two to six embryos were transferred to give a better chance for at least one to implant in the uterine lining and continue development and gestation. However, this led to increased multiple pregnancies (including high-order multiple gestations), which is a health risk to both the mother and the babies. In this circumstance, some practitioners recommend "multifetal pregnancy reduction" to end the lives of some of the fetuses and "reduce" the pregnancy down to no more than two. While this might reduce maternal risks to some extent, multifetal pregnancy reduction can endanger all of the developing fetuses, does not completely eliminate risks associated with multiple pregnancies, and can have adverse psychological consequences for the mother.[97,98] Additionally, multifetal pregnancy reduction is clearly the intentional ending of human lives.

Current guidelines in the United States,[99] as well as in other countries,[100] limit the number of embryos transferred in each cycle. In the U.S., the recommendation is for only one embryo (single embryo transfer, SET) to be transferred in healthy young women, with two or at the most three embryos as a limit in older women, while women at the extremes of reproductive life may be offered up to a limit of four.

Embryo Disposition: numbers created, destroyed, frozen, transferred, born

The latest global estimate is that at least 12 million babies were born via IVF between 1978 and 2022.[101] Less well-known are the estimates of the number of embryos created that led to the 12 million births.

It has been estimated that the average blastocyst conversion rate (percentage of zygotes formed in vitro that develop into blastocysts 5-6 days post-fertilization) is 66.7%[10] This means that 33.3% of the zygotes (one-celled embryos) do not proceed to the blastocyst stage in vitro.

Although we do not know for certain the rate of blastocyst conversion under natural conditions (in vivo), Jaris calculates that, under natural conditions, embryo loss is approximately 10-40% before implantation.[46] It also must be noted that there are cases in which the embryo starts to implant, but the woman never even knows she is pregnant.

The embryos that progress at least 2-3 days are graded for quality and either transferred to the mother, frozen, or discarded. Of those that are transferred to the mother, the majority do not survive. Embryo wastage is a term used to refer to the percentage of transferred embryos that do not result in the birth of the infant.[73] Embryo wastage rates have decreased from a high of 90% in 1995 to 76.5% in 2013.[73,74] Despite this improvement, nearly three in four transferred embryos do not survive to live birth. This is heavily dependent on the mother's age.

Embryos that are not transferred by fresh cycle are either discarded or frozen. "Fresh cycle" refers to transferring embryos created during the egg retrieval cycle and not freezing those embryos. "Frozen cycle" refers to the transfer of embryos previously frozen. One reference notes that an IVF clinic's optimal financial business plan is to harvest 15 eggs in a single "fresh" cycle and fertilize all eggs, knowing that embryos will be created in the process but not transferred in that fresh cycle.[102]

"Supernumerary embryos are expected."[102] The terms "supernumerary," "extra," or "leftover" are often applied to the human embryos created but not selected for fresh cycle transfer to the uterus. The high-quality embryos are sometimes frozen, perhaps for use in future transfers. Still, if their screening delegates them to a grade of low quality or genetically undesirable, the embryos are discarded. In many cases, a family will not transfer their remaining frozen embryos, regardless of their graded quality, once a desired number of children is reached. Embryos that don't meet desired characteristics are discarded, including in cases of embryo sex selection, which can lead to the disposal of healthy embryos.[103]

Cryopreservation is sometimes considered a life-sparing practice to preserve live embryos for future transfer. As with the number of embryos discarded, most clinics do not report the number of embryos they freeze. In 2003, the first survey of clinics found 400,000 embryos in freezers in the U.S.[104] A 2020 study indicated over 1.2 million embryos were then in

storage freezers.[105] Some estimate that there are now 1.5 million embryos in freezers in the U.S. alone.[106]

Theoretically, those judged as "high-quality" embryos have a better chance of implantation and gestation to birth, which is the endpoint for grading. However, studies show that even so-called "low-quality" embryos can develop into normal babies. Mosaic embryos are embryos that contain both euploid and aneuploid cells on prenatal genetic testing. Although they have a lower implantation rate, mosaic embryos are capable of producing normal infants.[107] The current practice is for most clinics to transfer mosaic embryos.

It is difficult to estimate the number of embryos created to result in the 12 million live births from IVF. Data from the Human Fertilization & Embryology Authority (HFEA) in the UK indicate that in that country, 1.7 million embryos created for IVF have been thrown away, and only 7% lead to pregnancy.[108,109] The HFEA has longitudinal data about the pregnancy rate per embryo transferred, which improved over the time of their data collection but has never exceeded 1 out of 3 embryos transferred (approximately 35%).

If we assume the best scenario of a 35% birth rate per embryo transferred worldwide, then achieving the 12 million estimated births from IVF necessitated the creation and transfer of, at the very least, 34 million embryos. This means that at least 22 million embryos who reached the capacity to transfer did not survive. And this 22 million does not include the embryos who died, were discarded, or were frozen and not transferred.

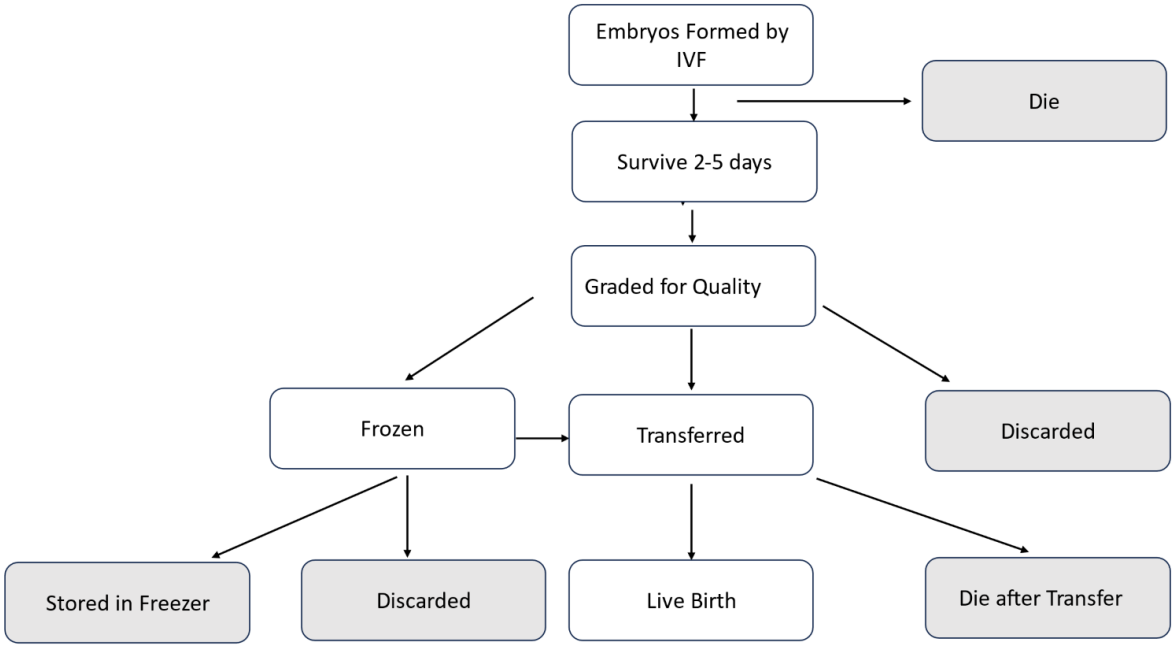

Figure 3 – Outcome of Embryos Created by IVF

As can be seen in Figure 3, there are multiple times in the process in which embryos do not survive, are discarded, or are frozen, possibly in perpetuity. As pro-life professionals who view all products of sperm-egg fusion as human embryos deserving of dignity and respect, the number of embryos that are created only to be discarded, die, or be frozen in perpetuity is concerning.

The survival of embryos after freezing is a significant concern. Cryopreservation involves protecting the embryo by infusing cryo-preservative into its cells, followed by either a slow freezing process or flash freezing (vitrification).[110] The process works because there are few cells in the young embryo, allowing the cryo-preservative to penetrate most cells and prevent damaging ice crystal formation. Theoregically, freezing at liquid nitrogen temperatures (-320°F/-196°C) can preserve embryos without cell degradation over long periods. However, some recent studies indicate that older embryos may suffer some damage from freeing, as well as from genetic testing.[111] The greatest danger is from ice crystals that form upon thawing, which destroys many embryos. Previously, a 50% survival rate after freezing and thawing was considered standard. More recently, for some clinics that use good techniques and care, survival rates in some cases can be up to 96%.[112] The disparity in survival rates after freezing means that freezing and thawing itself is technique-dependent, and poor technique can lead to the deaths of many embryos.

Some parents of frozen embryos offer their embryos for adoption or donation to other infertile couples. As a result, instead of lying dormant in a freezer, some of these embryos have been born.[113] In other cases, couples may designate that their frozen embryos be thawed and discarded. Frozen embryos that are abandoned and unclaimed may also be discarded.[114] In other cases, embryos are donated for research, where they are destroyed through experimentation.

Rarely, IVF has also been used to create embryos as “savior siblings.” Embryos are created by parents of a born child who has a lethal diagnosis, with the idea that a healthy, genetically-matched embryo can be gestated and this sibling, once born, can be an adult stem cell donor or even a tissue donor.[115] All of the other embryos either remain in frozen storage or are discarded.

There are life-sparing techniques that could be employed for IVF procedures. These include:

a. prohibiting the destruction of human embryos,
b. limiting the number of embryos created per cycle based on age and embryo survival rates in culture,
c. limiting the number of embryos transferred with each cycle, consistent with current ASRM guidelines,[99]
d. including the use of single-embryo transfer (SET), and
e. limiting embryo freezing.

Natural-cycle and minimal-stimulation IVF, which utilize no or minimal added hormonal boost, show consistently good data for Live Birth Rate and overall IVF success. Several studies have contradicted the assumption that more oocytes lead to better success; the advantages of decreased risk to women from ovarian hyperstimulation are significant. These milder IVF protocols are also less costly than traditional IVF.[8,116-120]

Another proposal is to couple life-sparing practices of IVF with egg-freezing rather than embryo-freezing. Freezing eggs does not obviate all ethical concerns but poses fewer potential problems than embryo freezing.[121]

Final Considerations

In summary, the recognition of human beings in the embryo stage calls for an ethical reevaluation of both research practices to conform with international consensus statements on human subject research and some practices in the ART/IVF industry. Our common humanity requires justice and beneficence for all human beings, regardless of age or circumstances of our beginnings.

Human beings conceived in vitro by scientific bioengineering are no less human than those conceived in vivo by natural processes. Therefore, they have the same moral significance and require the same bioethical considerations. IVF embryos are human beings and should be regarded as such, not as commercial products. The current legal status of embryo dispute cases, where embryos have been conceived in IVF, is determined under property law, treating the embryos as commercial property. Recognition of the humanity of the human embryo will require embryo dispute cases to be determined under family law, recognizing that there is a disposition in the best interests of the embryo. Parents must retain legal oversight and responsibility for their children, even when those children are still tiny, vulnerable embryos. Parents themselves deserve legal protection as the guardians of their children. Parents deserve full informed consent. Parents should retain legal recourse for the negligent loss of their children as embryos.

Summary of Recommendations and Conclusion

This committee opinion is intended to promote the dignity and life of the human embryo and promote the reduction of harms and risks to the embryo. AAPLOG does not endorse a formal position on the practice of IVF and acknowledges that there is a diversity of opinion among its members due to the ethical challenges in ART. AAPLOG does take the position that embryo destruction during the process of IVF is unethical.

For Assisted Reproductive Technology, we recommend the following:

1. Before attempting IVF, all women should receive complete informed consent, and every effort should be made to utilize restorative reproductive medicine as a treatment for infertility.

2. All human embryos deserve dignity and respect. Given the loss of embryos from freeze-thaw and the sheer number frozen in perpetuity, AAPLOG discourages freezing of embryos.
3. Only procedures that offer the prospect of direct benefit to the embryos or pose a minimal risk should be allowed.
4. Freezing of eggs does not carry the same moral implications as freezing of embryos and should be encouraged over freezing of embryos.
5. The number of eggs inseminated should be limited depending on the patient's age and intended family planning.
6. The number of embryos transferred each cycle should be limited according to current ASRM guidelines.
7. PGT in all forms (PGT-A, PGT-M, PGT-Translocation) should be discontinued.
8. Selective reduction of embryos or fetuses for multifetal pregnancies should be discontinued. Selective reduction is the intentional destruction of human life. Instead, the number of embryos transferred should be limited to diminish the ethical dilemmas of multifetal pregnancies.
9. Encourage minimal stimulation or natural cycle protocols for IVF.
10. Embryo Adoption should be encouraged as an ethical and compassionate alternative to discarding them or experimenting on them.
11. Deliberate destruction of embryos by any means is unethical.
12. Since human embryos are human beings and not objects, embryo dispute cases should be settled under family law, not property law.
13. Regulatory oversight of the IVF industry is sorely needed. Transparency provides accountability. Transparency and mandatory reporting of all data regarding IVF and ART practices, including the number of embryos created, transferred, destroyed, discarded, or cryopreserved, and patient outcomes, should be legally required.
14. Long-term data on health outcomes of ART should be a research priority (including mothers, babies, egg donors, and surrogates).

For Research, we recommend the following:

1. An immediate worldwide moratorium on the creation of both nonintegrated and integrated Human Embryonic Models (HEMs) should be instituted.
2. The creation of human embryos for research should be prohibited.
3. Creation of embryos other than by means of the fusion of a human sperm and a human egg should be prohibited.
4. Manipulation, where a human embryo is intentionally created or modified to include a heritable genetic modification or intentionally exposed to teratogenic materials, should be prohibited.
5. Any proposed research on embryos should conform to the international consensus guidelines on human sub-

ject research, including requirements that the study design ensures that human embryos are not the subject of destructive, harmful, or deforming research.

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