Research on human embryos

Joseph G. Schenker

Department of Obstetrics and Gynecology, Hadassah University Hospital, Jerusalem, Israel

Human; Embryo

Introduction

In the last few years medical science has made dramatic advances through research of the embryo and fetal tissue. Academic and medical benefits may be achieved from preembryo and embryo research, but at the same time, most people share fears of the threatening social results of free, unrestricted research on potential human beings.

Preembryo is defined as the period from fertilization until 14 days, till the appearance of primitive streak. Fertilization is not a single event, but a process which includes the penetration of sperm through the oocytes covers, fusion of male and female pronuclei, and formation of the zygotes. At the second day, the zygote cleaves to form two blastomeres, forming morula at the fourth day and than the blastocyst that starts the process of implantation. The term embryo is applied to the period from 2 weeks until 6 weeks. During this period organogenesis takes place, and at the end of this period – 42 days after fertilization – the embryo is fully formed. The term fetus is applied to the period from 42 days until delivery. Newborn is applied when the fetus is out of the mother's body.

Clinical indications for human preembryo research

Benefits from human preembryo and embryo research can be achieved in the four major medical areas:

(a) Infertility research – in order to improve clinical results.
(b) Diagnosis of genetic aberrations and possible therapy.
(c) Contraceptive research.
(d) Therapeutic use of embryonal tissue for transplantation in life threatening medical conditions.

The potential sources of preembryo for research are:

(a) Existing surplus preembryos from IVF.
(b) Defective IVF preembryos.
(c) Aborted preembryos or embryos obtained by flushing methods (in induced or spontaneous abortions).
(d) Creating preembryos for research.

Correspondence: J.G. Schenker, Department of Obstetrics and Gynecology, Madassa University Hospital, Jerusalem, Israel.

The most important indication for preembryo research from the clinical point of view is to improve the clinical results. The survey prepared by us for the IVF Congress in Jerusalem 1989 shows the following data: Until January 1989 there were 704 units operating in 52 countries, most of the IVF units are in Western Europe. The number of units per population differs from continent to continent and from country to country, i.e., IVF units in China – 1 unit per billion compared to 1 unit per 200 000 in Israel.

The world results for 1987, which include 40% of the units practising IVF performed above 50 000 cycles of IVF treatment and above 32 000 transfer cycles. These treatments resulted in 5937 clinical pregnancies and 3899 live births. The pregnancy rate per treatment cycle was 11.6%, the pregnancy rate per transfer cycle 16.5%; live birth per treatment cycle was 7.5% and live birth per transfer cycle 10.6%. The clinical abortion rate is still high, 9%, and the rate of live birth per pregnancy is only 64%.

Early pregnancy loss

Only 25% of clinical pregnancies occur from conception in vivo and in vitro. The 75% failure may be presented as biochemical pregnancies, early miscarriages and missed abortions. The exact causes of these pregnancy losses are unknown.

A failure of totipotential blastomeres to differentiate may be attributed to the mechanism of early pregnancy loss. Some cultured human blastocysts lack an inner mass. Human preembryos and embryos are apparently very prone to abnormal development, and this can also account for the very high loss of preembryos before the stage of implantation. Disturbance in hormone production by the early embryo may account for its failure to implant.

Improvement of clinical results

Improvement of clinical results can be obtained by better laboratory techniques, which can be achieved by preembryo research according to the following directions:

(a) Biochemical analysis of preembryos.
(b) Metabolic studies which will reveal the nutritional requirements of the preembryo.
(c) Determination of enzymatic activity.
(d) Determination of RNA synthesis.

The clinical results of IVF techniques can be improved on by further research of preembryo cryopreservation in the following directions:

(a) At which stage to freeze preembryos – pronuclear, morular, blastocysts?
(b) What cryoprotectant should be used?
(c) What method of freezing should be applied – progressive, rapid or ultra-rapid?
(d) Improvement of the methods of cryostorage and thawing.

The possibility to find a method of oocyte cryopreservation in the future will significantly improve the clinical results on the one hand, and on the other hand deminish the ethical, legal and religious problems which are involved with preembryo cryopreservation.

Micromanipulation and male infertility

About 40% of the causes of infertility may be attributed to the male factor. The conventional methods of male infertility therapy and even the practice of IVF have only limited success. Recently, in our department, we applied the zona drilling method in cases of male infertility, still without clinical results. The other methods in micromanipulation that can be applied are micro-injection of spermatozoa under the zona pellucida and microinjection of spermatozoa into the ooplasma.

Contraceptive research

Research on the human preembryo can also be contributed to the world problem of population control. New methods of contraceptives and early abortive techniques can be studied along the following directions:
(a) Contraceptive vaccine.
(b) Gamete and preembryo specific antigens.
(c) Anti-zona pellucida antibodies.
(d) Blocking maternal receptors for embryonic hormones.

Human embryo research for diagnosis of genetic aberrations and future therapy

About 1–2% of newborns are born with severe genetic defects. Genetic diseases, either directly or as precursors, account for a high proportion of serious handicaps in children and young adults. The advantage of in vitro diagnosis of genetic diseases in that the preembryo may be used as a diagnostic tool for early detection of genetic aberrations and prevent the need for CVS or amniocentesis later.

Over the last years a remarkable advance in genetics was made by applying molecular biological methods to the mapping of chromosomes, and identification of DNA sequences in a single cell, including human spermatozoa. Analysis of DNA in a single spermatozoa or in a single diploid cell would help in identifying defected genes as well as analysing the human genome. Attempts have been made to assess the preembryo's condition without direct interference with the embryo by using a method to analyse its culture medium. The methods for preembryo genetic screening may be:
(a) Applying DNA probe in situ hybrid formation.
(b) Biopsy of the preembryo.
Several studies have already been performed on preembryos
(a) Activation of embryonic RNA has been established.
(b) Phenotypical expression – transcription occurs in the human preembryo at cell stage 4.
(c) It is possible to apply a DNA probe to distinguish between a male and a female preembryo and to diagnose sex-linked diseases. These probes can be used for sex selection of preembryos.
Gene therapy in the future may be applied for therapeutic purposes in the preem-

bryonic stage and in the newborn, using genetic engineering by using the following methods:

(a) Somatic gene therapy.
(b) Gene line therapy.
(c) Eugenic genetic engineering.

Somatic gene therapy results in the correction of genetic disorders in somatic cells, and should be beneficial to the replacement of defective or missing enzymes in some metabolic disorders. It has already been applied in a case of severe combined immunodeficiency disease. The technique involves the following stages: removal of the patient's bone marrow, introduction of a normal gene, using retrovirus vector and reimplantation of the corrected bone marrow cells to the patient. This method of using a retrovirus has potential risks to the patient – serious infective disease or even developing malignant conditions. In our institution an attempt was made to use this method for the treatment of thalassemia. In our department we have attempted twice to perform bone-marrow transplantation to the fetus in utero.

Up to now, gene line therapy has only been performed in mammalian species. This technique consists of the insertion of a gene into the gametes or zygotes by using micromanipulation methods – injection of DNA; it has a high failure rate, and can produce delaterious results, because there is no control over the injected DNA and it is of limited usefulness in genetic disorders.

Eugenic genetic engineering means the insertion of a gene into a normal individual with the intention of enhancing a known characteristic. It may endanger the individual by changing the balance of the individual's cell or even the entire body.

Potentially, genetic engineering can be introduced for eugenic selection, resulting in an attempt to alter human traits such as personality, intelligence, human body etc.

Ectogenesis

Embryo research may lead to the creation of a human being without the necessity to use the uterus for implantation. It is required to close the gap between 20–22 weeks of pregnancy in which the immature newborn can be kept in an incubator, and the possibility of the embryo growing in vitro by developing an artificial placenta.

Ethical consideration

Modern medical ethics are based on multidisciplinary and pluralistic approaches to the philosophical, sociological and legal perspectives developed over the past four decades, especially influenced by the horrors of the 2nd World War.

When performing experiments on preembryos, one should take the following aspects into consideration:

(a) Respect for human dignity.
(b) The slippery-slope argument.
(c) Autonomy rights of the patients.
(d) Benefits.

The central question regarding the ethical problem of preembryo research is the moral status of the preembryo. There are three options for the definition of the moral status:

(a) The preembryo is an integral part of the mother's own body.
(b) The preembryo is a potential human being.
(c) The preembryo has the full status of a human being.

According to the option that the preembryo is an integral part of the mother's body, the mother has the right to abort the preembryo and to permit research on it in accordance with the Helsinki declaration.

The consequences of the definition that the preembryo has the full status of a human being are:

(a) Preembryo has its own rights.
(b) The interest of the mother are irrelevant to the future of the preembryo.
(c) There is no justification for induced abortion for maternal sake.
(d) The mother is regarded only as the guardian or procurator of her preembryo.

The definition that a preembryo is a potential human being is a new philosophical entity that compromises between the other two definitions, and is the one accepted today. Even though the preembryo is a potential human being it should be handled with dignity and its rights should be kept as long as they do not harm major social and maternal interests or other interests.

A basic decision should be made as to the question of when the status of a potential human being is acquired:

(a) At conception.
(b) When implantation occurs.
(c) With the appearance of the primitive streak.

It is almost impossible to reach a definite consensus about such an issue. Acceptance of the definition that the status of a potential human being is acquired with the appearance of the primitive streak resolved most of ethical questions concerning preembryo research so far.

The legal status of the preembryo

The legal status of the preembryo is difficult to establish. If one suggests it is a person, or even potential person, it has no legal status according to the law in most countries. There is a suggestion that the embryo is property, and by this definition it offends ethical principles. The above suggestions leave open the legal question of the right to use, to dispose, to sell and to purchase an embryo. A preembryo or embryo seems not to be a human being for purpose of criminal law. Deliberate destruction of a preembryo is not a criminal abortion act.

Juridical protection for a preembryo may be difficult to achieve, except through specific legislation.

The legal status of the preembryo is broadly discussed in the history of our civilization when the question of compensation for causing miscarriage is discussed. According to the Babylonic Code, compensation for destruction of an embryo/fetus was paid according to the social status of the pregnant woman. According to the Old Hebrew law, compensation was paid according to the severity of the damage.

The Hites Code states that compensation should be paid according to the state of gestation.

The Old Testament has been translated from Hebrew to Greek by the Jewish Community of Alexandria, Egypt. A mistake was made in the translation of Exodus by using the concept of 'form' related to fetus. Therefore the Greek law states that if the fetus is destroyed before it achieves its 'formation', 42 days, compensation should be paid. But, if the fetus is destroyed after 42 days, after it is fully formed, it should be regarded as human being and life should be given for life. The Latin version of the Bible has its origin in the Greek translation and so the above concept was accepted by the Christians. Only in 1869 the declaration of Pope Pius IX changed this concept to the present one that the preembryo/embryo acquires its protection of life from the moment of conception.

Islamic law graded the reparation concerning miscarriage and damage to the fetus according to the stage of gestation. It should be mentioned once again, that according to the International Law, the fetus acquires its legal status at birth.

The modern assisted reproductive technologies, including preembryo research, are presently practiced by one of the following systems:

(a) Legislation
(b) Governmental regulations.
(c) Regulations prepared by professional bodies.
(d) Local Helsinki Committees.
(e) Own standards.

According to our survey, research on preembryos is practised in only 13 countries. According to the legislation in some countries, such as Germany, Norway, Switzerland, Ireland, Israel etc., research on embryos is forbidden.

About 100 Ethical Committees' reports from different countries have dealt with the issue of assisted reproductive technologies, including research on embryos. The most important reports are from the following Committees: The Walter Committee in Australia, The European Human Reproduction Society (ESHRE), American Fertility Society, and the European Parliament.

The British Warnock Committee suggested that preembryo research should be permissible on embryos up to 14 days. The project should be supervised and authorized by special authorizing bodies. Even though this suggestion was not accepted by the legislation in U.K., research on embryos in Britain is conducted under the supervision of a professional body.

There are differences of opinion among the various ethical committees concerning the issue of embryo research, but all of them agree that the following procedures should be forbidden:

(a) Cloning.
(b) Inter-species fertilization.
(c) Genetic manipulations.
(d) Transfer of human embryo to another species.

Religious aspect of preembryo research

Our survey in 1989 showed that even in countries where the religious parties have no political power, the religious attitude of the population of religious groups

influences the practice of assisted reproduction, particularly the issue of research on preembryos.

The Jewish attitude

(a) It should be allowed to create/induce in vitro preimplantation embryo for fertility research if there are real chances that the sperm owner may benefit and have a child as a result of this research.
(b) Jewish law forbids destruction and use of the preembryo as long as it has the potential ability to be implanted.
(c) An in vitro blastocyst that hatched from its zona pellucida and lost its implantation potential may be kept for continuous research.
(d) It is prohibited to use a post-implantation preembryo for research, unless the research is essential for saving the embryo's life.
(e) The arbitrary period of the 14 days limit approved for research on preembryos by some ethical committees is not recognized by Jewish law.

The Christian view

Christianity recognizes the preembryo as a human being from the stage of conception. Any research on the preembryo is forbidden.

The Islamic law

Some Islamic schools may accept performing research on excess embryos resulting from IVF in order to increase their 'ILM'. It may be permissible in cases when it is for the sake of the individual embryo.

The Buddhist view

Buddhists believe that there is a continuity from life to life through many appearances. According to many Buddhist scholars experimentation on preembryos is acceptable.

The Hindu view

Hindu does not view that the soul, 'Atman', is having a specific beginning or specific end. It may be permissible, when it is to help the infertile couple and it serves the 'Dharma' of the physicians.

In conclusion, research on preembryos may broaden our basic knowledge on the development of the preembryo and embryo, improve the therapy of infertility, control of reproduction and genetic screening and potential therapy. However, on the other hand, many ethical, legal, social and religious problems are involved.