Article

A zygote is not an embryo: ethical and legal considerations

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Abstract

In spite of several past attempts at defining the point at which conception can be considered completed, resulting in the formation of an embryo, the existing definitions are still contradictory. In the absence of clear terminology, the application of laws aimed at the protection of early human life may have inadequate consequences for the efficacy of the current techniques of human infertility treatment. In this paper biological arguments are revisited, suggesting that the only point at which a clear demarcation line between what is and what is still not an embryo can be drawn is the moment of nuclear syngamy at the outset of the first cleavage division. The term 'zygote' is suggested to denote entities composed of spermatozoon and oocyte components before nuclear syngamy. It is suggested that the current embryo protection laws should not concern the zygote stage: at this stage, the main features that are said, in documents issued by different ethical and legal authorities, to characterize the early human embryo, namely the inseparable union of the male and female contribution, cell division and an autonomous control over cell division, are still not present. This reasoning strictly applies to embryos of biparental (paternal and maternal contribution) origin and cannot be extrapolated to embryos created by cell nuclear transfer (cloning). The application of embryo protection laws from the nuclear syngamy stage onwards can regulate embryo and embryo-derived stem cell research while still preserving the current high standard and efficacy of infertility treatment, which is of immediate interest to millions of infertile couples throughout the world.

Keywords: *assisted reproduction, early life protection, embryo, ethics, infertility treatment, law, zygote*

Introduction

Since the birth of the first child conceived by IVF (Steptoe and Edwards, 1978) the moral and legal status of the early stages of human post-fertilization development has been a widely debated issue which has become particularly controversial recently in relation to the development of new, non-conventional techniques, such as nuclear transfer, and methods of embryo creation. such as stem cell research (Bahadur, 2003; Bosch, 2003; Edwards, 2003; Hoffman *et al*., 2003; Schenker, 2003). In spite of the existing differences in the approach to this question in different countries, related to different cultural and religious backgrounds, there is a nearly general consensus that the early stages of human post-fertilization development are owed respect as a symbol of future human life (European Society of Human Reproduction and Embryology (ESHRE) Task Force on Ethics and Law, 2001).

Biologically speaking, the early post-fertilization development is a gradual process in which it is extremely difficult to define discrete landmarks that could serve to distinguish stages to which more moral importance should be attached than others. As nicely demonstrated in a recent parliamentary debate in the UK (Bahadur, 2003), the stage at which attribution of special rights for protection are claimed ranges from the moment of conception to 14 days post-fertilization.

In fact, it is still not clear which stages of development the term pre-implantation embryo (pre-embryo) should be used for, and the definition of fertilization or conception as a single time-point is biologically impossible (Nielsen *et al*., 2001). Yet it is just these terms that are used in laws regulating assisted

reproduction and derived biomedical interventions in all countries where a specific legislation on these subjects exists. Consequently, most of these texts are burdened with logical contradictions, and their strict application is virtually impossible.

The aim of this paper is to contribute to the definition of the stage from which the early human life is no longer a union of potentially separable paternal and maternal contributions and becomes a distinct individual which can be a subject of legal protection under the terms of national legislations referring to the entity called 'embryo'. It is hoped that this contribution will stimulate a debate from which clear rules, applicable in current clinical practice, will emerge.

Examples of different approaches to the definition of early embryo status

The Human Fertilisation and Embryology Authority (HFEA), which oversees legislation on assisted reproduction in the UK, states that the status of embryo should be given to 'a live embryo where fertilization is complete' and, in another place, that 'fertilization is not complete until the appearance of a two cell zygote'. However, references to an embryo in documents issued by the same authority sometimes also include 'an egg in the process of fertilization' (Nielsen *et al*., 2001).

In the Spanish Law of Assisted Reproduction (Ley 35/1988, 1988), 'embryonic development' is defined as 'that development which begins from the moment of fertilization and ends by birth'; the term 'pre-embryo' in the same law refers to a particular period of embryo development, and denotes 'the group of cells resulting from progressive division of the ovum from fertilization to approximately 14 days later, when it nidates in the uterus after the process of implantation started 5 days earlier and when the primitive streak makes its appearance'.

In Germany, the status of the embryo is defined by the Embryo Protection Law of 1990 (Embryonenschutzgesetz – EschG, 1990) which defined the embryo as 'a fertilized egg from the time of pronuclear fusion'. Because, under normal conditions, pronuclear fusion is immediately followed by the first embryonic mitotic division, the fertilized ovum (zygote) at the one-cell stage is not protected by this law.

In other countries, the embryo is not defined by a law, but there is a more or less general consensus on the terminology. In the USA, for instance, fertilization is defined as the union of male and female gametes which leads to the formation of a zygote. When a zygote divides, it becomes what is called a 'pre-embryo'; this term is used until approximately 14 days after fertilization when the development of the primitive streak begins and the pre-embryo becomes an embryo (Veeck, 1999).

According to the position held by the Catholic Church 'from the time that the ovum is fertilized, a life has begun which is neither that of the father nor of the mother; it is rather the life of a new human being with his (her) own growth' (Pope John Paul II, 1995) The definition of the developmental stage from which the early human life deserves legal protection will certainly be even more difficult in situations in which both fertilization and the zygote stage are bypassed in the process of embryo creation, such as for embryos resulting from cell nuclear replacement techniques using nuclei from diploid somatic cells (House of Lords, 2003). This issue will require independent focused deliberations, and it should be stressed that the arguments used in this paper are restricted to the natural situation, for embryos of biparental origin.

Common points

In spite of the existing contradictions, the above examples draw attention to several major characteristics that are commonly used to define the embryo in western societies. These can be summarized as three points: firstly, inseparable union of the paternal and maternal contribution, secondly, cell division and thirdly, autonomous control over the processes of cell division and differentiation. How do these characteristics apply to borderline stages at the beginning of a human life?

The union between the paternal and maternal gametes is usually called fertilization or conception, and it is a continuous process, not a unique time-point. It is thus necessary to use a single well-defined event in this process as a landmark for any definition of the embryo using fertilization or conception as the starting point. The beginning of fertilization is defined vaguely, since the events preceding spermatozoon penetration of the oocyte, namely the complex interactions of the spermatozoon with the oocyte vestments, called the cumulus oophorus and the zona pellucida, are usually also considered to be integral parts of the process of fertilization. However, these events are not indispensable for the outcome of fertilization and can be bypassed when fertilization is achieved by means of currently available micromanipulation techniques.

Moreover, an oocyte undergoing the process of fertilization does not represent either a physical union of the paternal and the maternal genome or a functional unit of the paternal and maternal contribution to development. In fact, the respective parental genomes are completely separated with the male and the female pronucleus. The male pronucleus, which has developed from the spermatozoon nucleus, can be easily removed from the fertilized ovum by a simple manipulation, and it can be replaced with another one. It can therefore be suggested that the term 'zygote' should be reserved for the period from the beginning of a physical, more-or-less stable union between the spermatozoon and the oocyte to nuclear syngamy. In these conditions it does not appear sensible to protect the pronuclear zygote on the basis of the fact that it would potentially mark the origin of a genetically unique individual, provided that the two pronuclei eventually fuse. If this kind of potentiality were accepted as a sufficiently strong argument for zygote protection, paradoxical consequences would ensue. For instance, when oocytes are fertilized by intracytoplasmic sperm injection, the unique genetic constitution of the potential embryo is decided at the moment at which the biologist makes the selection of the spermatozoon to be injected. This uniqueness is irreparably destroyed if he decides not to use the previously selected spermatozoon and to replace it with another one.

The first time that an inseparable physical unification of the male and the female genomes is achieved is nuclear syngamy

(pronuclear fusion), which is shortly followed by the first mitotic division of the fertilized oocyte. Beginning with this moment it is technically impossible to separate the paternal and maternal contributions both of which become merged in a unique entity which can survive or die but always as one entity. The time span from the beginning to the end of nuclear syngamy is not known exactly. However, in normal human development the time between nuclear syngamy and the beginning of the first mitotic division must be very short, because a syngamy nucleus, an entity resulting from the fusion of the male and the female pronucleus, is seen extremely rarely when living human oocytes are checked for signs of fertilization, unless immature male germ cells (spermatids) are used for fertilization (Tesarik and Mendoza, 1996; Barak *et al*., 1998).

As for the autonomous control of the embryo over its own growth and differentiation, it appears even later in development. The first cell cycle of the fertilized oocyte is completely dependent on the oocyte developmental programme which is activated by a relatively non-specific stimulus delivered by the fertilizing spermatozoon. In fact, the same stimulus can be delivered artificially by physical (electric discharge) or chemical (ionophores, ethanol) agents, and oocyte activation can also can occur spontaneously, in the absence of fertilization (Gook *et al*., 1995). The development of such oocytes, referred to as parthenogenetically activated ones, and that of normally fertilized oocytes occur in a quite similar way during the time period corresponding to the interval between spermatozoon penetration and syngamy of the fertilized oocytes.

In view of these facts it can be concluded that oocytes in the process of fertilization (zygotes) do not have characteristics that are generally attributed to entities called 'pre-implantation embryos' or 'pre-embryos' until nuclear syngamy (pronuclear fusion) which is the end-point of fertilization. Consequently, embryo-protecting laws should be applied to fertilized oocytes only from nuclear syngamy onwards.

Consequences for infertility treatment efficacy

If an embryo is defined as an entity resulting from nuclear syngamy, and thus clearly distinguished from the fertilized oocyte or zygote, laws aimed at the protection of early embryos from voluntary wastage would achieve the goal of preventing the uncontrolled commercial use of human pre-implantation embryos for stem cell research. In fact, stem cells cannot be derived from fertilized oocytes that have not yet undergone cell division. On the other hand, the application of such laws would not harm infertile patients attending infertility clinics for an assisted reproduction attempt.

German experience (Ludwig *et al*., 2000) shows that infertile couples can be given efficient assisted reproduction treatment even under conditions of absolute embryo protection. Accordingly, no embryo can be voluntarily destroyed under the German Embryo Protection Law (1990), and all decisions as to the number and choice of embryos to be eventually transferred must be taken before syngamy. Yet, techniques are currently available that enable a reliable prediction of a zygote's capacity to form a good-quality embryo (Scott and Smith, 1998; Tesarik and Greco, 1999; Tesarik *et al*., 2000). Moreover, the application of selection techniques at the zygote stage before syngamy has recently been shown to reduce the risk of the formation of chromosomally abnormal embryos (Coskun *et al*., 2003; Gámiz *et al*., 2003).

The distinction of the terms 'zygote' and 'embryo' has acquired new significance recently as laws extending the degree of pre-implantation embryo protection are to be applied in some European countries. This is the case in Spain and Italy where the respective parliaments have voted modifications of the existing law (Spain) or the introduction of a new law (Italy) aimed at a more efficient protection of the early human life, especially with regard to the risk of embryonic cell abuse by unjustified disposal in the development of newly emerging stem cell techniques. This more restrictive legislature appears to reflect a new kind of fear aroused in the European populations by the recent multiplication of announcements of biotechnological performances and developments for which, in the future, early human embryos are claimed as a source of 'raw material'. Importantly, potential future applications of such techniques would be outside the field of infertility diagnosis and treatment, which appears to make them publicly less acceptable than embryo research activities carried out in the past, which were self-directed and concerned the same patients, or at least the same category of patients, whose embryos were sacrificed. The current switch to 'non-reproductive' research on human embryos is often perceived as 'instrumentalization' of early human life, which might ultimately lead to deliberate creation of human embryos with the sole purpose of their later destruction. The current legal restrictions of human embryo research appear to be a kind of reaction to this potential menace.

Many reproductive scientists actually consider the current political efforts at increasing the degree of legal protection of early human embryos to be over-exaggerated. Such individuals would obviously not agree with moral distinctions between the steps of human conception similar to those suggested in this paper. In fact, it can be argued that the price to be paid for a compromise reached on this basis would be quite high: namely, that embryo research and embryonic stem cell research should be given up in exchange for being legally allowed to maintain the current high standard and efficacy of infertility treatment. Even though this objection can be understood and the potential interest of these issues is evident, it is not possible to escape the conclusion that linking infertility treatment with those new research ambitions into a single pack to be fought for in the current legal battles would, in a sense, transform patients currently seeking infertility treatment into hostages whose medical assistance, which is currently permissible, is put at risk in the name of hypothetical future possibilities of helping other patients in indications that are often unrelated to infertility. Personally, as 'infertility doctors', the authors will always clearly prefer the defence of the former group of patients' interests. The suggestions contained in this paper are based on this standpoint.

Conclusion

In conclusion, clear definitions are needed to apply laws protecting early human life against abusive destruction. The definition of the pre-implantation embryo as an entity resulting

from fertilization at the completion of nuclear syngamy is based on objective scientific arguments, and its broad acceptance would enable the formulation of coherent and easily applicable laws which could efficiently regulate techniques leading to embryo destruction without compromising the right of infertile patients to be given an adequate treatment. The term 'zygote' is proposed for earlier periods beginning with the physical union between the spermatozoon and the oocyte until nuclear syngamy is achieved. It is suggested that zygotes do not deserve any form of legal protection.

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Received 22 March 2004; refereed 30 March 2004; accepted 28 April 2004.