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REVIEW

Fate of fertilized human oocytes

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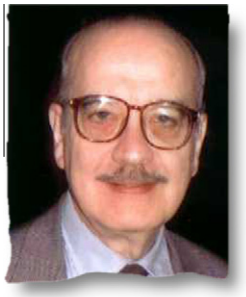

Professor Giuseppe Benagiano is the Dean of the Post-graduate School of Gynaecology and Obstetrics, University 'la Sapienza' in Rome. Here, he became professor in 1980 and acted as Director of the First Institute of Obstetrics and Gynaecology during 1982–1993. He was nominated Director of the Special Programme of Research in Human Reproduction of WHO in 1993 and became Director General of the Istituto Superiore di Sanità in 1994. He has studied, Karolinska Institute, Stockholm and Population Council, Rockefeller University. His long-standing interest is hormonal contraception and he pioneered the use of GnRH analogues for gynaecological disorders of endocrine origin, such as endometriosis, adenomyosis and leiomyomata.

Abstract Establishing the proportion of fertilized oocytes and early human embryos that proceed to term may help policy makers in their evaluation of when the life of a new human individual begins and in determining the nature of protection to be accorded to it. The rate of spontaneous abortions, although increasing with age, overall does not exceed 15%. However, abortion rates refer only to 'clinical pregnancy', whereas early embryonic loss is more common than generally believed. Evidence of such wastage comes from many sources. Human fecundity rarely exceeds 35% and may be decreasing due to deterioration in semen quality. Embryological studies show that 50% of randomly recovered preimplantation embryos have severe anomalies. The study of sensitive markers of pregnancy, such as human chorionic gonadotrophin, indicates early embryo wastage in the order of 50%. Pregnancy wastage may be a function of the time lapse between ovulation and implantation as the implantation window extends between menstrual cycle days 20 and 24. Finally, data obtained with natural IVF cycles also indicate major losses, with an overall pregnancy rate of 7.2% per cycle and 15.8% per transfer. These data, however, are biased by a high cancellation rate and low oocyte retrieval in natural IVF cycles.

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Introduction

'When exactly does a new human life begin?' is probably the most fundamental question of reproductive biology. It is a question that permeates every aspect of bioethics of human reproduction and to which very different responses have been provided, depending on the philosophical or theological starting point selected. Assisted reproduction technologies, preimplantation genetic diagnosis (PGD), embryo freezing, emergency contraception and other recent advances in reproductive biology, such as use of cybrids for the prevention of diseases based on mitochondrial disorders and the use of chimeras have moved the debate on the definition of the beginning of human life from theoretical discussion to practical application (Benagiano et al., 2010). An answer to the question has now also become legally relevant in view of the need felt in most countries to regulate assisted reproduction treatment producing legislation that,

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even implicitly, utilizes some kind of definition of the status of a human embryo.

One aspect of the problem that often seems to go unnoticed is what happens physiologically to a fertilized oocyte, because the public generally assumes that, once fertilization has taken place, most oocytes easily progress until they reach the stage of a viable fetus. This presumption is based on the clinical observation that spontaneous abortions after the 12th week of gestation, although increasing with age, in younger women do not exceed 15%. Miscarriage rates range from about 10% at age 20 to 50% at age 40–44 and more than 90% for women 45 years of age or older (Nybo Andersen et al., 2000).

At close scrutiny however, the situation is much more complex, since abortion rates refer only to what is usually called clinical pregnancy, namely a pregnancy in which an ultrasound scan demonstrating an embryonic heart action, has confirmed definitively that a woman is pregnant. During the 2–3 weeks that precede the recognition of a live embryo, i.e. an ongoing gestation, much can happen and, indeed, evidence has been accumulating that early embryonic loss among fertile women is much more common than lay wisdom believes.

Over the last 50 years, a number of scientific publications have produced evidence of different nature showing a major pre-clinical human pregnancy wastage. As far as is known, this is the first systematic review of this evidence, which is of complex nature and from many sources. It is, therefore, hoped to provide a useful summary of present knowledge of the fate of a zygote/embryo in the first 2 weeks of its existence.

The importance of this information lies in the fact that, when debating ethical issues related to the beginning of a new human life, biological facts must be taken into consideration, because whereas biology cannot alone answer the question, no correct answer can be given if one ignores biological facts. It is proposed to hold such a debate in a subsequent paper, with the help of experts in bioethics.

Assessing embryo loss after fertilization

Currently, there are many observations, scientific experiments and objective data which demonstrate the existence of significant wastage of human fertilized ova and early embryos during the first 2 weeks after fertilization (i.e. before the first period is missed). This evidence is relatively new, because, until the middle of the 20th century, common wisdom believed that – since congenital anomalies at birth are fortunately rare (Khaury, 1989) – conception was almost universally followed by the development of an embryo and then a fetus that, in the great majority of instances, would reach term and result in the birth of a healthy child. The reason for this major difference of opinion is methodological: 50 years ago, wastage could only be measured by establishing the total rate of miscarriages which, in many demographic surveys, did not exceed 15% and in some cases indicated even lower figures (Bocciolone et al., 1989). These percentages are influenced by maternal age and genetic and environmental factors, but if one considers only miscarriage of clinical pregnancies including late miscarriages, the inevitable conclusion appears to be that at least 80–85% of all conceptions become a viable fetus.

Today it is known that the situation is much more complex and, before reaching any conclusion, a number of important potentially confounding variables must be analysed.

Human fecundity

When calculating early pregnancy it is necessary to take into account human fecundity, defined as 'the probability to produce a vital term newborn per menstrual cycle during which there was normal sexual activity' (Olsen and Rachootin, 2003). Data collected in the last few decades indicate that human fecundity rarely exceeds 35% and, even under ideal conditions, the greatest probability of achieving a clinical pregnancy per cycle is around 30–40% (Balakrishnan, 1979; Charbonneaux, 1970; Henripin, 1954; Sheps, 1965; Slama et al., 2002; van Noord-Zaadstra et al., 1991; Vessey et al., 1976; Wang et al., 2003; Zinamen et al., 1996; **Table 1**).

Although successful human reproduction may be influenced by factors like the incidence of infertility in a given population, clearly there is a major discrepancy between the frequency of fertilization and that of implantation, miscarriage and live birth.

Table 1 Human fecundity: the proportion of women who will deliver a term baby per menstrual cycle during which there were frequent acts of non protected intercourse.

Population studied	*Publication*	*Fecundity index*
France, 17th and 18th centuries	Charbonneaux (1970)	0.21
Peru, 20th century	Balakrishnan (1979)	0.17
Mexico, 20th century	Balakrishnan (1979)	0.21
USA, 20th century (Hutterite sect)	Sheps (1965)	0.28
Canada (Québec), 18th century	Henripin (1954)	0.31
Great Britain, 20th century (pluriparous women trying to conceive)	Vessey et al. (1976)	0.21
USA, 20th century	Zinamen et al. (1996)	0.30
The Netherlands, 20th century after 12 months and age 31	van Noord-Zaadstra et al. (1991)	0.54
China, 20th century	Wang et al. (2003)	0.40

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