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Review Article

Natural Causes for Low Human Fertility

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Abstract

Despite the efforts to improve the conditions of gamete and embryo culture, the success rate of assisted reproductive techniques in humans is limited. This suggests that the reduced embryo potential could not be a result only of suboptimal *in vitro* conditions, but real features of oogenesis and early embryogenesis are involved. Low developmental potential of embryos is related to high rate of chromosomal abnormalities. The chromosomal segregation errors are based on disturbance of interactions between chromatin, cytoskeleton and other factors involved in the last stages of mammalian oocyte meiosis.

Keywords: Mammalian oocyte; Meiosis; Preimplantation embryo; *In vitro* fertilization; Aneuploidy

Abbreviations

IVF: *In Vitro* Fertilization; IVM: *In Vitro* Maturation; ART: Assisted Reproductive Techniques; aCGH: Array Comparative Genomic Hybridization

Introduction

Studies on early mammalian embryogenesis started with the work of Carl Hartman. In 1931, he published his observations on bovine preimplantation embryos obtained by oviductal flushing [1]. Later, a similar approach was applied to obtain oocytes and preimplantation embryos from other mammalian species with easily predictable or controllable oestrus with multiple ovulations – rabbits, rodents and ungulates [2-5]. The techniques of human IVF (*in vitro* fertilization) were based on these investigations. Studies of mammalian oocytes and preimplantation embryos became the base for development of assisted human reproduction, as well as for fundamental investigations of human oogenesis and early embryogenesis.

Limited Success Rate of IVF

In vitro fertilization was developed as an approach for treatment of human infertility. However, its introduction was soon followed by disappointment of the relatively limited success rate of the method. It was initially assumed to be a result of suboptimal conditions of *in vitro* culture systems, hormonal stimulation and techniques for oocyte aspiration. Hence, efforts for improving success rates were directed towards optimization of these factors. A major step in the development of ART (assisted reproductive techniques) was provided by the introduction of gamete manipulations. As a result of their application, the success rate of ART was brought close to that of natural conception–according to current official data of ESHRE, the success rate of ART in European clinics is approximately 30%, and this proportion has remained stable [6,7]. Moreover, even this rate is due to the fact that in each treatment cycle, typically 2 or 3 embryos were transferred into the uterus. Now, it is accepted that the chance for each embryo to be implanted is approximately 15% [8,9]. These facts indicate that the potential to improve the success rate of ART, though not yet exhausted, is limited. Hence, the decisive factor for the treatment success must be some natural characteristics of the embryo.

Morphological Defects of Preimplantation Embryos

The most obvious abnormality of human IVF embryos is the high rate of morphological disorders – cell fragments, differences in blastomere size, enucleated and multinucleated cells, apoptotic-like cells and inadequate blastomere number are observed in more than half of the embryos [9-12]. These data can be summarized in Table 1. For the last decade, elaboration of culture and manipulation techniques has not brought significant improvement of these data.

Cytogenetic Abnormalities of Human Oocytes

The first published cytogenetic study of human oocytes was performed by Edwards, 1968, and of human embryos by Angell, 1983 [13,14]. The metaphase state of ovulated mammalian oocytes facilitates karyotyping of unfertilized eggs because pretreatment with cytostatic is not required. Data accumulated so far indicate that a substantial part of oocytes derived both by natural and stimulated ovulation, carry numerical chromosomal anomalies. In different periods, different authors have published widely varying aneuploidy rates for human oocytes unfertilized after IVF. If extreme values are excluded, the reported percentages of aneuploid oocytes are between 25% and 35% [15,16]. Although data about human oocytes obtained after natural ovulation are scarce, they are very similar to those mentioned above [17]. Data for non-primate mammals show substantial differences – their rate of meiotic chromosomal abnormalities is ten times lower than those observed in human [18], while oocytes of rhesus monkeys and marmosets produce results similar to those of humans [19,20]. Therefore, it is assumed that chromosomal anomalies of human oocytes are not a methodological

Table 1: Morphological defects of preimplantation embryos.

Morphological abnormality	Embryos able to form blastocyst
Cell fragments occupy up to 15% of the volume of cleavage embryo	33 %
Cell fragments occupy more than 15% of the volume of cleavage embryo	17 %
The number of blastomeres – more than expected	28 %
The number of blastomeres – less than expected	14 %

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artifact but are associated with natural imperfection of primate female meiosis. It was initially hypothesized that abnormal oocyte karyotype would prevent gamete fusion, but this was not confirmed [21]. Rather, chromosomal errors in the embryo, which are in most cases oocyte-derived, interfere with its potential for post-fertilization development. It can become evident as failure of implantation or at an even later stage, as spontaneous abortion.

Cell Cycle Control

Cell cycle control machinery in eukaryotes prevents the completion of cell division in cells which do not fulfill a set of criteria. These control mechanisms are universal and evolutionary conserved. However, in mammalian meiosis the division control shows some uncommon features – first, its efficiency is not full, and second, the efficiency is different for males and females.

Numerical chromosome aberrations are observed in 10-25% of human fetuses. Nearly 80% of them are due to errors during metaphase-anaphase transition of the first meiotic division in oocytes [18]. They are result of prematurely segregated bivalents or sister chromatics, unnoticed by the cell cycle control.

The meiotic checkpoint responsible for the exactness of metaphase I- anaphase I transition (spindle checkpoint) corresponds to the mitotic checkpoint which permits anaphase onset after estimation of spindle integrity and chromosome-tubulin interactions. Meiotic spindle checkpoint is supposed to arrest chromosomally abnormal oocytes at metaphase I, preventing their further maturation, fertilization and cleavage. But in oocytes the efficiency of the control during this passage is diminished (compared with male meiosis and mitosis). This fact is pointed out as one of the major reasons for human oocyte aneuploidy [22,18]. Chromosomal errors are possible also in spermatogenesis, but they are eliminated by the cell cycle control far more effectively. For example, several point mutations in mice, which cause malsegregation of bivalents, in males lead to apoptosis of spermatocytes with abnormal karyotype. In female mice these mutations do not diminish the number of ovulated oocytes, but increase the proportion of aneuploid oocytes [22]. A type of male infertility in human is associated with presence of monovalents at metaphase I and lack of progress to metaphase II, which is a result of effective spindle control. It is proved that the efficiency of the control in females is not full both for hormonally stimulated ovulation and natural cycles. Experimental data for mouse show that the efficiency of the spindle checkpoint depends on genetic background (mated mouse strains) and on the oocyte maturation conditions [18,23].

Cell cycle control is relaxed also during the first zygotic mitoses. This is illustrated by the following facts: the proportion of chromosomally abnormal embryos exceeds that of aneuploid oocytes; blastomeres with chromosomal anomalies divide normally and can be seen also in embryos without morphological defects; the high level of mosaicism shows that segregation errors arise with high probability in each of the mitoses until 16-cell stage and the morula compaction. It is supposed that normal cell cycle control is established during the morula-blastocyst transition.

Aneuploidy Rate in Human Preimplantation Embryos

In human embryos obtained *in vitro*, aneuploidies, mosaics of diploid and aneuploid cells, polyploidy and haploidy have been registered [10,14]. For cleavage stage embryos, it has been observed that the level of chromosomal errors is about three times higher in embryos with morphological defects – 37% vs. 12% for morphologically normal embryos [14]. In the late 1980s, the rates of embryonic aneuploidy reported by different authors varied widely. This could be explained by the small number of embryos studied and by the low efficiency of classical karyotyping used at that time. The mean percentage of cleavage stage embryos with chromosomal errors found till then was 23% [24]. As with oocytes, it was observed that chromosomal anomalies are more frequent for human early embryos than for those of other mammals. For example, in mice this rate varied between 3% and 21%, and in investigated domestic animals it was between 7% and 10%. After introduction of FISH for cytogenetic testing of blastomeres, data for human embryos varied between 15% and over 85%. This great discrepancy was due to differences in embryo cohorts included in the studies – embryos with or without morphological defects, with progressing or arrested divisions, and originating from different groups of patients [8,25,26]. The data can be summarized as follows:

-The percentage of chromosomally normal embryos is unexpectedly low.

-A substantial proportion of chromosomally abnormal embryos are mosaic.

-There is a correlation between karyotype errors and developmental potential of preimplantation embryos, but it is not absolute – embryos with severe chromosomal disorders are able to form morphologically normal blastocysts. After CGH was adapted for single blastomeres, it was shown that ¾ of human preimplantation embryos contain at least one chromosomally abnormal blastomere [27]. The currently accepted data are as follows: about 25% of embryos have normal chromosomal set, 7-20% are uniformly aneuploid, 6% are polyploid, 0,6% are haploid, 40-50% are mosaic and at least 5% are chaotic (mosaics of blastomeres with different chromosomal defects). Most chromosomally abnormal embryos are mosaics of diploid and aneuploid and/or polyploid blastomeres [25,28-31]. The frequencies of different types of mosaics are as follows:

16% - 2n/chaotic chromosomal configurations;

15% - 2n/4n, rarely another polyploidy;

14% - 2n/aneuploidy for one or more chromosomes;

3% - 2n/n.

There are data that in women under 35 years, mosaic embryos are more than uniformly aneuploid embryos [32]. It is hypothesized that in young women, embryonic chromosomal errors arise more often at a post zygotic stage, while in older women the contribution of meiotic errors is more important.

Data about chromosomal disorders in preimplantation embryos are summarized in [33-35]. Discrepancy in the reported percentages is probably due to differences in patient and embryo groups.

Natural Selection of Embryos with Normal Chromosomal Set

One of the approaches to improve implantation rate after IVF is the

blastocyst transfer preferred by some fertility centers. An argument in favor of this approach is the fact that the majority of chromosomally abnormal embryos are naturally eliminated before reaching blastocyst stage [36]. It is now known that if mechanisms for natural selection of high-quality embryos exist, they are not based solely on karyotype normality. Some uniform trisomies and monosomies are compatible with blastocyst formation – at least 20% of human chromosomally abnormal three-day embryos reach blastocyst stage [33]. According to different authors, between 20 and 47% of early human IVF blastocysts are chromosomally abnormal. Results have been obtained by array comparative genomic hybridization (aCGH) for all 24 chromosomes. It has been proved that the rate of chromosome errors in the inner cell mass and the trophectoderm cells is nearly the same [33]. That means that the trophectoderm biopsied cells are a good predictor for the embryo ploidy. It was reported that the implantation rate is significantly higher when blastocysts are tested by aCGH [37].

In general, the correlation between morphological characteristics and developmental potential to blastocyst, on one side, and chromosomal aberrations, on the other, is not absolute. Hence, the selection of embryos with good morphology or advanced to blastocysts increases the probability that the embryos to be transferred will have normal karyotype but does not guarantee it.

Origin of Meiotic Abnormalities in Oocytes

Mammalian oocyte meiosis begins in the fetal ovary but is arrested before the end of prophase I. Meiotic resumption in oocytes is coupled to a complex of hormonal and paracrine stimuli and requires precise synchronization of follicle and oocyte maturation. Disturbances in this elaborate system can cause meiotic abnormalities, including numerical chromosomal aberrations. Despite the clinical importance of aneuploidies, little is known about the molecular mechanisms leading to them. These mechanisms can be genetic, epigenetic and cytoplasmic.

Genetic Background

There are several findings which support the role of genetic factors in abnormal chromosomal segregation:

-Generally, segregation errors in early mammalian embryos affect all chromosomes with equal probability. However, there is an exception: the Y chromosome of a particular mouse strain, designated as Wt-Y chromosome. Its non-disjunction rate is 50% in embryos till 16-cell stage, after which the segregation of Wt-Y becomes normal. In hybrids of Wt males with females from different strains, non-disjunction rate of Wt-Y chromosome varies widely [38].

-In some human populations, Down syndrome is 4 times more frequent in children of consanguineous marriages, indicating importance of still unidentified recessive mutant alleles [39].

-In some IVF-treated families, very high percentages of chromomally chaotic embryos have been observed [32].

-The number of unsuccessful IVF procedures for a particular family is positively correlated to the aneuploidy level of their investigated surplus preimplantation embryos [40].

-The proportion of aneuploid embryos obtained from a particular family during different IVF cycles is almost constant. Hence, the chromosomal status of embryos derived from one IVF cycle can be used as a prognostic criterion for the next procedures of this family [40].

Cytoskeletal Disorders

Rearrangement of oocyte chromosomes is mediated by cytoskeletal elements. The role of microfilaments and microtubules has been analyzed in many studies [41] but little is known about the role of intermediate filaments in this process. During meiotic resumption, oocyte is in dictyate, with a large nucleus traditionally called germinal vesicle (GV). The dictyate-metaphase I transition begins with GV breakdown and assembly of meiotic spindle. The mechanism of this assembly is quite different from those operating in mitosis and male meiosis. Oocyte chromatin has the leading role in organizing the spindle. Small tubulin asters are formed around each bivalent. They fuse to form a bipolar spindle at the center of the oocyte. A fine actin spindle-like structure is formed together with the tubulin spindle and overlying it. It is connected to the cortical actin and helps to move the spindle towards the oolemma [42-44]. Then, meiotic spindle is anchored under the membrane by the so-called actin cap, which is involved also in the rotation of the spindle and the polar body extrusion [45].

Other Factors

Besides DNA and cytoskeletal proteins, huge numbers of other factors are involved in chromatin and cytoplasmic rearrangements. In recent years, many of them have been identified as molecules and their action has been characterized [46]. These factors can be classified into the following groups: proteins responsible for DNA condensation (condensins) [47]; proteins participating in sister chromatid cohesion and conjugation of homologous chromosomes (cohesins); proteins controlling crossing over; elements of kinetochore complex; motor proteins (kinesins, including chromokinesins) participating in spindle assembly and chromosome alignment at its equator, which are connected to microtubules, kinetochores and chromosomal arms [48]; cyclin and cyclin-dependent kinases, responsible for the cell cycle control [49]; ATPases and proteinkinases [50,51], associated with mentioned factors; hormonal signals.

The chromatin, cytoskeleton and associated factors must act as a skilled orchestra and each false tone can result in meiotic errors. It is supposed that meiotic disturbances and low fertility chance in some apparently healthy women (and especially aged women) is related to the lack of synchronization between the factors that direct oogenesis.

Models for Studying Human Oocyte Meiosis

The first question here is what kind of model cells should be applied to investigate the causal factors of final steps of human oogenesis – from the resumption of meiosis to the ovulation. Mitotic studies are not adequate model for studying meiotic malsegregation because of some fundamental differences – meiotic chromosomes are organized in bivalents, sister chromatids have a common kinetochore and do not separate at anaphase I. The usefulness of male meiotic models is also limited, because meiosis in mammalian oocytes is further complicated in several ways: meiotic prophase I starts in the fetal ovary and the process is arrested for a long time (even years) at dictyate stage; the oocyte meiotic spindle is organized without

centrosomes by association of multiple tubulin asters; polarization of the oocyte cortical cytoplasm and asymmetric cytokinesis require rearrangement of microfilament cytosketon; the cell cycle control is less effective in oocytes than in spermatocytes. Even most of mammalian oocytes have limitations as models for studying the finale steps of human oogenesis. Most used species have too many evolutionary differences with human – the lifespan, the length of the reproductive lifespan, length of preimplantation period, different rates of oocyte aneuploidy, etc. Hence, animal oogenesis models should be applied carefully for human oocytes. The model systems closest to human are primates.

The next question is how to provide sufficient number of non-human primate oocytes for research without ethical complications. The answer is *in vitro* maturation (IVM) of monkey oocytes obtained from surgically removed ovaries.

What We Know from Primate Oogenesis

Nichols and co-workers [20] demonstrated that that IVM can induce meiotic anomalies in macaque oocytes, especially those obtained from older females. Reported levels of hyperploidy for *in vivo* ovulated oocytes was below 5%, while for IVM oocytes it was 25% for young and over 50% for old monkeys.

Morphologically normal *in vitro* produced rhesus macaque embryos were tested using a five-color fluorescent in situ hybridization [52]. Approximately 50% of embryos were normal, 18% were aneuploid, and approximately 31% were mosaic; nearly half of tested blastomeres were euploid for tested chromosomes.

Delimitreva and co-workers [19] have investigated the meiotic abnormalities in *in vitro* matured marmoset oocytes. Normal haploid chromosome number of 23, X was observed in 63% of karyotyped oocytes. Abnormal karyotypes were noticed only in oocytes obtained from small follicles. For another group of MII oocytes, where meiotic spindles were visualized, only half of the MII oocytes displayed well-formed spindles and apparently correct chromosomal alignment.

Later, the same working group has analyzed the relationships between variations in the organization of microtubules, microfilaments, and chromatin in metaphase I and metaphase II marmoset oocytes arrested during *in vitro* maturation and fertilization [44]. It was demonstrated that improper chromosomal condensation was associated with both abnormal microfilament and microtubule arrangement. This was further associated with abnormal actin organization, disorientation and late stabilization of microtubules, but not related to abnormal organization of spindle poles. Chromosomal misalignment was associated with disorientation and late stabilization of tubulin, but not to broad spindle pole. Additionally, abnormal actin polarization appeared not to be related to abnormal spindle poles.

Conclusion

We can conclude that the limited success rate of IVF (and *in vivo* conception) is based on some natural features of human oogenesis and early embryogenesis. The cell cycle control of the final steps of oocyte meiosis and the first zygote mitoses is prone to errors which result in a high rate of numerical chromosome aberrations. Moreover, the correctness of chromosomal segregation depends on coordinated action of the genome, chromatin proteins, cytoskeleton fibers, hormones, etc. The most appropriate models to investigate the causal natural factors of low human fertility are non-human primate oocytes and early embryos.

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