Symposium: Genetic and epigenetic aspects of assisted reproduction

Meiotic errors in human oogenesis and spermatogenesis

Renée Martin is a Professor of Medical Genetics in the Faculty of Medicine, University of Calgary, Canada. She is a fellow of the Canadian College of Medical Geneticists and was president of the college in 1997–1998. She has also been very active in the Canadian Fertility and Andrology Society, and was president from 1992 to 1993. She is an executive board member of the Preimplantation Genetic Diagnosis International Society. Dr Martin's research focus is on the causes of chromosome abnormalities in humans, with a particular focus on human sperm. She holds the Canada Research Chair in Genetics and was recently elected a fellow of the Canadian Academy of Life Sciences.

Dr Renée Martin

Renée H Martin
University of Calgary, Department of Medical Genetics,
3330 Hospital Drive NW, Calgary, Alberta, Canada T2N 4N1
Correspondence: e-mail: rhmartin@ucalgary.ca

Abstract

Chromosome anomalies are extraordinarily common in human gametes, with approximately 21% of oocytes and 9% of spermatozoa abnormal. The types of abnormalities are quite different since most abnormal oocytes are aneuploid, whereas the majority of abnormalities in spermatozoa are structural. Chromosomes 21 and 22 (the smallest chromosomes) are over-represented in aneuploid gametes in both oocytes and sperm. Chromosome 16 is also frequently observed in aneuploid oocytes, whereas the sex chromosomes are particularly predisposed to non-disjunction in human sperm. Maternal age is clearly the most significant factor in the aetiology of aneuploidy; theories about the cause of the maternal age effect are discussed. Paternal age does not have a dramatic effect on the frequency of aneuploid sperm; there is some evidence for a modest increase in the frequency of sex chromosomal aneuploidy. Meiotic recombination has a significant effect on the genesis of aneuploidy in both females and males. New techniques, which allow the analysis of recombination along the synaptonemal complex, have yielded interesting new information in healthy and infertile individuals. There is a link between infertility and the genesis of chromosome abnormalities. Future studies will unravel more of the underlying causal factors.

Keywords: *aneuploidy, human chromosome abnormalities, human oogenesis, human spermatogenesis, meiosis, non-disjunction*

Introduction

Meiotic errors are extraordinarily common in humans, with the frequency of chromosome abnormalities at least an order of magnitude higher than in other animals. The incidence of chromosomal anomalies is approximately 0.6% in newborns, 6% in stillbirths, and 60% in spontaneous abortions. Most chromosome abnormalities are lethal and are lost early in embryologic development, manifesting as infertility or spontaneous abortions. Some chromosomal abnormalities survive to term, for example, trisomies 13, 18, 21, aneuploidy for the sex chromosomes, and certain chromosomal rearrangements. Individuals with these chromosome anomalies can have mental and physical disabilities, infertility, as well as behavioural problems and impaired sexual development.

The cause of the difference in the incidence of chromosome abnormalities between humans and other species is unknown, but it is clear that the majority of errors are generated during meiosis. Thus, it is profitable to study the causes of chromosome abnormalities and factors affecting their frequency by studying human gametes. During the past few decades, there has been an explosion of research on the aetiology of chromosome abnormalities in both females and males. This is largely because of the availability of human oocytes and embryos from IVF, preimplantation genetic diagnosis (PGD) and new technologies allowing access to the human sperm chromosome complement.

Both human oocytes and spermatozoa are susceptible to numerical and structural chromosome abnormalities, but it is clear that the majority of numerical errors (aneuploidy) occur during oogenesis and that these lead to the greatest burden in humans (Hassold and Hunt, 2001).

Oogenesis

Incidence of chromosome abnormalities

A number of studies on oocytes surplus to requirements from IVF programmes have demonstrated that approximately 20% of oocytes have numerical abnormalities and 1% have structural abnormalities (**Table 1**) (Martin *et al.*, 1991; Plachot, 2001; Pellestor *et al.*, 2002). Thus, oogenesis is particularly susceptible to producing aneuploid gametes. The majority of these studies are on infertile patients who have been treated with hormones; thus, the frequencies might be considered overestimates. However, some studies on oocytes from unstimulated cycles have generated similar estimates (Volarcik *et al.*, 1998). Nevertheless, these figures should be considered maximal estimates. The error causing aneuploidy can occur in either the first (MI) or second (MII) division of meiosis, but for most chromosomes MI errors predominate (Hassold *et al.*, 1996; Kuliev *et al.*, 2002). In all likelihood, this relates to the fact that the first division of meiosis begins prenatally (when the female is a fetus) and then undergoes a state of suspended animation until meiosis resumes just before ovulation. This quiescent state may last 10 years or 50 years, and is clearly associated with more errors as the state is prolonged (Risch *et al.*, 1986; Sandalinas *et al.*, 2002; Munné *et al.*, 2006).

Distribution of aneuploidy

All chromosomes are susceptible to error during oogenesis, since aneuploidies for all chromosomes have been described in human oocytes (Pellestor *et al.*, 2002; Rosenbusch, 2004) and spontaneous abortions (Hassold, 1980; Hanna *et al.*, 1997). In oocytes and early embryos, both hypohaploid (nullisomic) and hyperhaploid (disomic) chromosome complements are observed (Martin *et al.*, 1991; Pellestor *et al.*, 2002). However, in spontaneous abortions and newborns, essentially only one monosomy (45,X0) is observed with any frequency (Hassold *et al.*, 1996). Thus, most monosomies must be lethal during early embryogenesis, probably before implantation. The chromosomes most frequently observed in aneuploid metaphase II oocytes (Kuliev *et al.*, 2002; Pellestor *et al.*, 2002; Sandalinas *et al.*, 2002; Rosenbusch, 2004) are the D, E, and G group chromosomes with chromosomes 21, 22, and 16 being the most frequent in most studies (**Table 1**). Thus, the small chromosomes are more susceptible to meiotic errors.

Non-disjunction or predivision

For many years, it was assumed that non-disjunction (in which homologous chromosomes do not disjoin at meiosis I or sister chromatids do not separate at meiosis II) was the cause of aneuploid gametes. However, in 1991 Angell reported single chromatid errors in meiosis II metaphases from human oocytes (Angell, 1991). She suggested that the chromatids had arisen as a result of premature division of the centromeres at meiosis I ('predivision'). Angell confirmed these preliminary results with further studies (Angell *et al.*, 1993; Angell, 1997) and suggested that predivision was the main cause of human aneuploidy. Subsequent studies on IVF oocytes using conventional cytogenetics (Pellestor *et al.*, 2002; Rosenbusch, 2004) and fluorescence in-situ hybridization (FISH) analysis (Dailey *et al.*, 1996; Kuliev *et al.*, 2002) have demonstrated that both classical non-disjunction and predivision are important causes of aneuploid oocytes. Dailey *et al.* (1996) cautioned that the frequency of balanced predivision of chromatids increased significantly with the time oocytes were in culture, suggesting an artefact of culture. However, this group has subsequently demonstrated that chromatid predivision is observed even in fresh non-inseminated oocytes that were fixed immediately after retrieval (Sandalinas *et al.*, 2002). New techniques allowing visualization of chromosome movement by a time-lapse culture system (Otsuki and Nagai, 2007) or analysis of the meiotic spindle by PolScope imaging (Rama Raju *et al.*, 2007) may provide novel avenues to investigate these errors.

Maternal age

Maternal age has long been recognized as the most significant factor in the aetiology of aneuploidy. Countless studies of human newborns, spontaneous abortions, early embryos, and oocytes have reaffirmed the significant effect of maternal age on the incidence of aneuploidy. The effect is dramatic: Hassold and Chiu (1985) have estimated that for women under the age of 25 years, about 2% of clinically recognized pregnancies are trisomic, whereas for women over 40 years of age, this frequency is approximately 35%. There have been many theories as to the cause of the maternal age effect. One early theory that has received recent attention has been the idea that delayed fertilization and oocyte ageing is the aetiology of the maternal age effect (since older women are presumed to have less frequent intercourse) (German, 1968; Sharov, 1991). However, a number of animal studies in various species have demonstrated that delayed fertilization of oocytes leads to polyploidy, not aneuploidy (Yamamoto and Ingalls, 1972; Ishikawa and Endo, 1995). Furthermore, the ovulated oocyte is at the metaphase II stage until fertilized. Thus, any effect of delayed fertilization could only account for non-disjunction during MII, yet the majority of errors occur during MI. Another theory suggested that older women had a less stringent selection against aneuploid fetuses, thus fewer chromosomally abnormal fetuses were aborted and, therefore, more were born (Ayme and Lippman-Hand, 1982). However, if it were solely a maternal selection issue, the paternal origin of the trisomic offspring would be immaterial. In fact, the effect of maternal age is only observed in cases of maternal origin; thus, it must be oogenesis that is the cause of the maternal age effect.

It has been suggested for many years that biological age, rather than chronological age, is a risk factor for aneuploid concepti (Brook *et al.*, 1984). Recent studies in humans lend credence to this hypothesis. Freeman *et al.* (2000) found that mothers of Down syndrome children had a significantly higher chance of having a reduced ovarian complement (because of ovarian surgery or congenital absence of one ovary) compared with controls. Similarly, Kline *et al.* (2000) found that the mean age at menopause was 0.96 years earlier in women with trisomic losses compared with women with chromosomally normal concepti. Recently, van Montfrans *et al.* (2002) found elevated basal FSH concentrations in women with a history of a Down syndrome pregnancy. These studies lend support to the idea that women with a reduced ovarian capacity have an increased risk of an aneuploid conception.