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COMMENTARY

Advanced maternal age at childbirth and the development of uniparental disomy. A commentary on the proportion of uniparental disomy is increased in Prader–Willi syndrome due to an advanced maternal childbearing age in Korea

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Advanced maternal age at childbirth (usually ⩾35 years old) is known to be a risk factor for the occurrence of non-disjunction at meiosis 1.[1] As non-disjunction at maternal meiosis 1 results in the generation of disomic oocytes and nullisomic oocytes, fertilization of such abnormal oocytes and normal sperms leads to the production of trisomic and monosomic zygotes. Although such aneuploidies are usually incompatible with life, several types of aneuploidies such as trisomy 21 could permit the production of livebirths. Consistent with this, the frequency of newborns with trisomy 21 obviously increases with advanced maternal childbearing age.[2]

It is predicted, therefore, that trisomy rescue type maternal uniparental disomy (UPD) increases with advanced maternal childbearing age. Indeed, this type of maternal UPD is produced by two steps: (1) the generation of a trisomic zygote between a disomic oocyte and a normal sperm; and (2) loss of an extra chromosome of paternal origin from the trisomic cell. The first step is a maternal age-dependent phenomenon, while the second step would be a by-chance phenomenon. In addition, fertilization of a disomic oocyte with a nullisomic sperm should also produce maternal UPD referred to as gamete complementation, although this must be an extremely rare event.

This notion has been examined by Whittington *et al.*[3] and Matsubara *et al.*[4] using Prader–Willi syndrome patients as a clinical model. Although disomic oocytes can be formed by non-disjunction either at meiosis 1 or meiosis 2, it is possible to distinguish between non-disjunction at meiosis 1 and meiosis 2 by detailed microsatellite genotyping (heterodisomy for pericentromeric loci is indicative of non-disjunction at meiosis 1, and the combination of isodisomy for the pericentromeric loci and heterodisomy for at least one middle to distal microsatellite loci is indicative of non-disjunction at meiosis 2).[5] Consequently, advanced maternal age at childbirth has clearly been shown to be a risk factor for the development of upd(15)mat mediated by non-disjunction at meiosis 1 in both UK and Japan. Furthermore, in this issue of the *Journal of Human Genetics*, Cho *et al.*[6] have also reported similar results indicating a positive relationship between advanced maternal age and the occurrence of upd(15)mat mediated by non-disjunction at meiosis 1 in Korea.

It is also predicted that monosomy rescue type paternal UPD increases with advanced maternal childbearing age. This type of paternal UPD is produced by replication (duplication) of a single paternally derived chromosome in a monosomic zygote generated by fertilization between a nullisomic oocyte and a normal sperm, and the generation of nullisomic oocytes at meiosis 1 is a maternal age-dependent event. In this regard, Kagami *et al.*[7] have studied Japanese patients with upd(14)pat, revealing a positive association between advanced maternal childbearing and the occurrence of monosomy rescue type upd(14)pat.

Furthermore, aneuploid oocytes can also be generated by sister chromatid pre-division during meiosis, in addition to meiotic non-disjunction.[1] As it is impossible to distinguish between sister chromatid pre-division and meiotic non-disjunction by molecular studies, its relevance to the development of UPDs remains unknown. Importantly, however, sister chromatid pre-division during meiosis is also known to increase with maternal age.[1] Thus, increased maternal childbearing age would contribute to the development of trisomy rescue type maternal UPDs and monosomy rescue type paternal UPDs, because of sister chromatid pre-division during meiosis.

These arguments would provide two implications. First, it is inferred that increased maternal childbearing age would also constitute a risk factor for the development of UPDs for multiple chromosomes. However, the studies on this matter remain insufficient, except for upd(15)mat and upd(14)pat.[3,7,8] Thus, further studies are necessary for UPDs of various chromosomes. Second, recent studies have implicated that assisted reproductive technologies (ART) may exaggerate the occurrence of imprinting disorders. Although most studies have focused on epimutations

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(hypomethylations),[9] UPD has also been reported in children born after ART, including the report by Cho *et al.*[6] in this issue. However, as ART is usually performed for aged couples, it is critical to take account of the maternal childbearing age in the risk assessment of ART.

In summary, delayed childbearing age is regarded as a predisposing factor for the development of not only aneuploidies but also UPDs. As childbearing age is becoming later and later especially in developed countries, it is essential to perform more extensive research and to provide appropriate medical information.

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