The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening

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Objective: To determine the relationship between the age of the female partner and the prevalence and nature of human embryonic aneuploidy.
Design: Retrospective.
Setting: Academic.
Patient(s): Trophectoderm biopsies.
Intervention(s): Comprehensive chromosomal screening performed on patients with blastocysts available for biopsy.
Main Outcome Measure(s): Evaluation of the impact of maternal age on the prevalence of aneuploidy, the probability of having no euploid embryos within a cohort, the complexity of aneuploidy as gauged by the number of aneuploid chromosomes, and the trisomy/monosomy ratio.
Result(s): Aneuploidy increased predictably after 26 years of age. A slightly increased prevalence was noted at younger ages, with >40% aneuploidy in women 23 years and under. The no euploid embryo rate was lowest (2% to 6%) in women aged 26 to 37, was 33% at age 42, and was 53% at age 44. Among the biopsies with aneuploidy, 64% involved a single chromosome, 20% two chromosomes, and 16% three chromosomes, with the proportion of more complex aneuploidy increasing with age. Finally, the trisomy/monosomy ratio approximated 1 and increased minimally with age.
Conclusion(s): The lowest risk for embryonic aneuploidy was between ages 26 and 30. Both younger and older age groups had higher rates of aneuploidy and an increased risk for more complex aneuploidies. The overall risk did not measurably change after age 43. Trisomies and monosomies are equally prevalent. (Fertil Steril® 2014;101:656–63. ©2014 by American Society for Reproductive Medicine.)
Key Words: Comprehensive chromosomal screening, embryonic aneuploidy, IVF, preimplantation genetic screening, trophectoderm biopsy

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Advances in clinical and laboratory practice have resulted in steady improvements in in vitro fertilization (IVF) outcomes over the last two decades. Although the enhanced outcomes are excellent and provide infertile couples with outstanding opportunities to build their families, the reality is that IVF

remains an inefficient process. Evaluation of the most recent Society for Assisted Reproductive Technologies (SART)/U.S. Centers for Disease Control and Prevention (CDC) data reveal that approximately 17% of fresh embryos deemed of sufficient quality to merit transfer actually progress to clinical pregnancy (1).

The inefficiency in IVF may result from many factors, but clearly one major issue is the age-related rate of aneuploidy (2). Aneuploidy is associated with maternal age and is only subtly related to the morphologic appearance of the embryo (3). As such, a real percentage of even the "most ideal" embryos selected for transfer are going to be aneuploid and have little if any meaningful reproductive potential (4).

The development of validated testing platforms capable of analyzing all 24 chromosomes has empowered clinicians, laboratorians, and scientists to assess the ploidy status of embryos before selection for transfer (5, 6). Accurate diagnoses combined with the substantively enhanced safety attained with trophectoderm biopsy (7) at the blastocyst stage have resulted in meaningfully increased implantation and delivery rates (4, 8).

These studies provide class I data for enhanced outcomes, but they apply to well-defined populations, with data condensed into relatively large age ranges. Clinical application of these technologies requires specific counseling of individuals from the general IVF population. Although an individuals' personal prognosis will be influenced by multiple factors, data on comprehensive chromosomal screening (CCS) results from the general population may be useful. Counseling regarding CCS generally occurs in two settings: before electing to proceed with CCS and again after the results of the analyses of their cohort are available.

Before initiating treatment, counseling typically includes at least three general considerations. First is the safety of the procedure itself. That issue has been addressed, and the safety of trophectoderm biopsy is reasonably established. The other two issues are what proportion of a patient's embryos are likely to be aneuploid, and what is the probability that all of her embryos will be aneuploid, leaving nothing available for transfer? These answers may need to be adjusted for each individual's circumstances, but age-specific data are most helpful.

After the results of the CCS analysis are available, there may be questions of whether those results are generally consistent with those of a woman's age-controlled peers. In addition to the overall rate of aneuploidy, it is possible to consider the nature of the aneuploid errors that are identified. This would include the complexity of the errors (i.e., did they involve a single chromosome, two chromosomes, or three or more chromosomes?). Also worthy of consideration is the overall ratio of trisomies to monosomies. The prognostic values of these factors for a single individual remain to be examined in detail, but they do provide some insight into the nature of the errors that that cohort of the embryo experienced. They may also be important for the clinician and embryologist when evaluating the performance of the assay being used for CCS across a larger number of embryos from multiple patients within their laboratory.

To date, there has not been a systematic report of CCS results in a large number of embryos from a general IVF population. Our study determined the relationship between maternal age and the aneuploidy rate, the no-euploid embryo rate per cohort, the complexity of encountered aneuploid errors, and the trisomy/monosomy ratio.

MATERIALS AND METHODS

Population

The embryos undergoing CCS of trophectoderm biopsies that were submitted to the Reproductive Medicine Associates (RMA) genetics laboratory for analysis were selected for the study. In our center, all patients are offered aneuploidy screening as a means to increase pregnancy rates, decrease loss rates, and decrease transfer order. All biopsies were reviewed, and the following information was collected: [1] the result of the genetic analysis, [2] the age of the woman producing the oocyte that resulted in the embryo being biopsied, and [3] the IVF program from which the biopsy was submitted. There were no inclusion or exclusion criteria beyond having those pieces of information available. The indications for CCS were categorized as family balancing, single-gene cases, recurrent pregnancy loss, and routine infertility care. Expanded blastocysts, equivalent to Gardner blastocele expansion score of 3 to 6, are biopsied for CCS.

Assays

The trophectoderm biopsy samples were placed into lysis buffer using a previously established protocol and were then submitted for evaluation. The samples were analyzed via quantitative polymerase chain reaction (qPCR) or single-nucleotide polymorphism (SNP) array using an established 24-chromosome assay that has been specifically validated for trophectoderm biopsies (5, 6). The results of each biopsy were initially categorized as being euploid or aneuploid. Among those embryos that were aneuploid, they were further categorized as having a single chromosome involved, two chromosomes involved, or three or more aneuploid chromosomes. Finally, the aneuploid result was further characterized as being either monosomic or trisomic. In the event that there were two or more abnormalities with one chromosome being monosomic and another being trisomic, the embryo was considered both monosomic and trisomic.

Data Analysis

The initial analysis was simply to determine the percentage of biopsy samples that were euploid and the number that were aneuploid relative to the age of the woman producing the oocyte. The data were stratified into single years of age. Subsequently, the data were grouped into the age groups used for reporting by SART, with the exception of the <35-years age group. Given the large number of years within that age group, the data were further divided into those oocytes where the female was younger than 26 years, 26 to 30 years of age, or 31 to 34 years of age.

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