Polymorphism on chromosome 21 does not affect ovarian reserve but clinical outcomes after *in vitro* fertilization treatments

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Study question. To assess the effect of polymorphic variants on chromosomes in female fertility and assisted reproductive treatment (ART) outcome.

Summary answer. Polymorphism on chromosome 21 affects oocyte and embryonic quality leading to worse gestational outcomes in women undergoing assisted reproductive cycle.

What is known already? Polymorphic chromosome variants are more common in infertile women and seem to influence clinical outcomes after an assisted reproductive treatment. Polymorphisms were considered as a variant when the chromosome region was greater or smaller than the same region on the homologous chromosome; as a minimum, twice the size on the other homologue. The apparently lower implantation and clinical pregnancy rates observed in female carriers has been related to a higher oocyte and embryo aneuploidy rate. However, not all authors find this negative effect, so it remains a controversial subject to date.

Study design, size, duration. This retrospective study was performed in 11 private clinics belonging to IVI group from January 2012 to December 2016. We included 985 women, of which 45.6% (n=449) had normal karyotype and were considered as a control group; 37.2% (n=366) were carriers of a polymorphism; and 17.3% (n=170) showed a chromosomal inversion. All women underwent a fresh autologous ICSI cycle. Statistical analysis was performed by ANOVA and chi-square where applicable.

Participants/materials, setting, methods. The cytogenetic study was performed by culture of peripheral blood lymphocytes stimulated with phytohemagglutinin and subsequent staining with trypsin-Giemsa (GTG bands). 15 metaphases were evaluated for each case and the banding resolution was 400–550 bands per haploid set. All cases were carried out according to the International System for Human Cytogenetic Nomenclature Guidelines.

Main results and the role of chance. Polymorphic variants for chromosomes 1 (46,XX,1qh+), 9 (46,XX,9qh+), 13 (46,XX,13ps+), 14 (46,XX,14ps+), 15 (46,XX,15ps+), 16 (46, XX,16qh+), 21 (46,XX,21ps+) and 22 (46,XX,22ps+) were included, as well as inversion of chromosome 9, being the most frequent 46, XX, inv(9)(p11q13). Basal data showed no differences among the three groups for the female ages, infertility years and days of stimulation, number of oocytes retrieved, number of metaphase II oocytes or number of transferred embryos. However, we observed statistical differences in antral follicle count between control group (3.2 ±0.7), polymorphism carriers (4.6 ± 0.7) and 9 chromosomic inversions (3.7 ± 1.0), p=0.008; and for the implantation rate being the results as follows 34.7%, 31.6% and 26.0%, p=0.048 for the control, polymorphism and inversion group respectively.

Focusing on chromosome 21 because its greater clinical relevance, we found that female characteristics were similar compared to the control group, and despite demonstrating a similar response to stimulation, significant differences were noted in implantation rate (35.3% vs. 44.4%, p=0.036); pregnancy rate (44.8% vs. 60.0%, p=0.008) and miscarriage rate (22.5% vs. 53.3%, p=0.005) between women with normal versus 21ps+ polymorphism karyotype, suggesting a higher embryo aneuploidy rate in these patients.

Limitations. Despite the advantages that our data set confer the analysis, limitations still remain. One consequence of a retrospective study is that not all pertinent risk factors are likely to have been identified and subsequently recorded. So only association, and not causation, can be inferred from the results.

Wider implications of the findings. Although the female carriers of the polymorphism on chromosome 21 have better implantation and pregnancy rates than women with normal karyotypes, the high miscarriage rates suggest a female aneuploid factor to be taken into account in women who are seeking pregnancy.

Study finding/competing interest. None

Trial registration number. It does not apply