# Embryo aneuploidy is not impacted by selective serotonin reuptake inhibitor exposure

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**Objective:** To study whether maternal exposure to selective serotonin reuptake inhibitors (SSRIs) has any influence on rates of blastocyst aneuploidy and/or in vitro fertilization (IVF) cycle outcomes.
**Design:** Retrospective cohort analysis.
**Setting:** Private and academic IVF center.
**Patient(s):** Patients who underwent IVF with preimplantation genetic treatment with trophectoderm biopsy (n = 4,355 cycles) and patients who underwent a single-embryo transfer (SET) between January-2012 and June-2017 (n = 2,132 cycles).
**Intervention(s):** Comprehensive chromosome screening and euploid SET.
**Main Outcome Measure(s):** Odds of embryo aneuploidy.
**Result(s):** Of 19,464 embryos analyzed, 3.9% (n = 743) were exposed to a SSRI, and the remaining 96.1% (n = 18,721) were not. The embryo euploid rate was 52.1%, and the aneuploid rate was 42.5%; 5.4% of the reports were inconclusive. No differences were found in clinical and IVF characteristics among the cohorts. After controlling for cofounders, there was no statistically significant associations between exposure to SSRIs and the odds of aneuploidy (adjusted odds ratio [OR] 0.04; 95% confidence interval [CI], −0.04–0.09). In a subanalysis including 2,132 thawed SET cycles, no differences were observed in implantation rate (71.3% vs. 70.1%; OR 0.60; 95% CI, 0.60–1.47), clinical pregnancy rate (58.2% vs. 59.7%; OR 0.70; 95% CI, 0.70–1.61), loss rate (18.5% vs. 11.49%; OR 1.54; 95% CI, 0.94–2.54), or multiple pregnancy rate (0.6% vs. 0; OR 0.7; 95% CI, 0.02–7.32) between cohorts.
**Conclusion(s):** Patients exposed to SSRIs in vivo are not susceptible to an increased rate of embryo aneuploidy in IVF. The IVF outcomes of patients exposed to SSRIs do not differ from those of unexposed patients. (Fertil Steril® 2017;108:973–9. ©2017 by American Society for Reproductive Medicine.)
**Key Words:** Aneuploidy, antidepressants, in vitro fertilization, preimplantation genetic screening, selective serotonin reuptake inhibitors

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Between 7% and 15.5% of American couples will be diagnosed with infertility (1), among whom 11% to 54% will experience a high-level of stress, anxiety, and depression before and/or during assisted reproduction technology (ART) treatment while undergoing in vitro fertilization (IVF) (2, 3). Although cognitive and behavioral therapies are the first-line treatments for anxiety/depression (4), many infertile patients are under pharmacotherapeutic treatments while pursuing reproductive treatment. Antidepressants are the most prescribed medications commonly used to treat depressive and/or anxiety disorders in persons aged between 18 and 44 years old (5). Although the severity of the depressive state dictates the choice and dosage used of the antidepressant, the most commonly recommended therapeutics include selective serotonin reuptake inhibitors (SSRI) (6).

It is well understood that serotonin, or 5-hydroxytryptamine (5-HT), plays a role in the pathophysiology of depression and anxiety. Low levels of 5-HT can be associated with sadness, anxiety, and worthlessness following a reduced function of the central serotonergic system and other monoamine systems (7, 8). Selective serotonin reuptake inhibitors function by inhibiting the reuptake of serotonin by blocking the specific transporters on the surface of the presynaptic neuron and increasing the levels of 5-

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HT in the synaptic cleft. A robust level of 5-HT in the synapse presents the opportunity for greater stimulation of the serotonin receptors on the postsynaptic cleft, which generates a mood stabilizing effect (9). The SSRIs available in the United States include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline (10).

The 5-HT transport system has been found to be expressed as early as the zygote and can extend to the blastocyst stage. Studies published by Khozhaĭ et al. (11) and Il'ková et al. (12) have demonstrated the regulation of embryogenesis to be influenced by serotonin exposure and the 5-HT transport system. In a study published by Kim et al. (13), fluoxetine exposure appeared to benefit the development of mouse blastocysts; yet when embryos were exposed to extreme levels of fluoxetine, growth was shown to be inhibited. The 5-HT receptor has also been found to be expressed in murine and mammalian embryos, and in these models the serotoninergic pathways regulate oocyte spawning and meiotic maturation (14).

As couples increasingly use IVF to assist in their reproductive goals, clinicians have the opportunity to obtain greater understanding of the interaction between 5-HT and embryonic developmental (15). A recent study by Kaihola et al. (16) evaluated cleavage-stage embryos exposed to 0.25 or 0.5 $\mu$M fluoxetine in the culture medium, and they observed rapid development and a shorter time for starting cavitation after thawing in embryos exposed to the higher level of fluoxetine. The investigators mentioned an unpublished pilot study in which extreme concentrations ($>$1.0 $\mu$M fluoxetine) statistically significantly increased embryo death, suggesting an exposure threshold has yet to be defined and a marginally adverse SSRI influence may exist for human embryo development (16). Aside from elucidating the optimal levels of serotonin and their impact on embryo formation (17), transduction signal pathways such as calmodulin-dependent protein kinase II (13) or regulation pathways involved in cellular growth and proliferation could be implicated in the observed embryonic developmental differences (18).

With the abundant use of antidepressants by infertile patients, understanding their potential effect on embryo development is paramount. Serotonin and its transport pathways have been observed to have an influence on embryogenesis, so it has been theorized that patient exposure to SSRIs during IVF treatment may adversely influence oocyte maturation or chromosome segregation in vivo. We investigated whether maternal SSRI exposure before IVF affects the rate of embryo development, especially as it pertains to blastulation and embryo ploidy status. Additionally, we performed a subanalysis to analyze whether SSRI exposure adversely affects ART pregnancy outcomes.

## MATERIALS AND METHODS

### Study Design and Patient Population

A single center, retrospective, cohort analysis of infertility patients studied those who completed an IVF cycle with preimplantation genetic screening (PGS) for comprehensive chromosome analysis with quantitative PCR and/or next-generation sequencing–based analysis from January 2012 to June 2017. A subsequent subanalysis evaluated the IVF outcomes of the patients who underwent a synthetic endometrial preparation and single-euploid embryo transfer (SET) from January 2012 to March 2017. Oocyte donor recipients were excluded from all analyses.

Exposure to SSRIs was defined as the regular use of any serotonin reuptake inhibitor medication at least 1 month before and throughout the patient's IVF controlled ovarian hyperstimulation (COH) or synthetic endometrial preparation cycle and continued after embryo transfer (ET) until discharge from the clinic around 12 to 14 weeks' gestation. Exposure was confirmed from patient self-report on a universal medication form, interviews by nurses and IVF coordinators, clinical electronic records during the treatment, and dispensation records.

### Stimulation Protocol

Patients underwent conventional COH for IVF as described previously elsewhere (19, 20). Oocyte final maturation was induced with recombinant human chorionic gonadotropin (hCG) alone (Ovidrel; EMD Serono) or with 2 mg of leuprolide acetate (Lupron; AbbVie Laboratories) concomitant with 1,000 IU hCG (Novarel; Ferring Pharmaceuticals) in patients at risk of ovarian hyperstimulation syndrome. Patients underwent vaginal oocyte retrieval under ultrasound guidance 36 hours after surge, and they were inseminated via intracytoplasmic sperm injection to allow genetic testing of the embryos.

### Laboratory Procedures

**Embryo culture and biopsy techniques.** Embryos were cultured up to the blastocyst stage as previously described elsewhere (19, 20). On day 3 of embryo development, all embryos underwent laser-assisted hatching via creating a 25–30 Mm opening in the zona pellucida with a 200–300 $\mu$s pulse ZILOS-tk Laser (Hamilton Thorne Biosciences) to facilitate posterior trophectoderm herniation.

Blastocyst trophectoderm biopsies were performed on day 5 and/or day 6 of development, contingent upon morphologic eligibility (Gardner-Schoolcraft classification $\geq$3BC). Biopsy was performed as described previously elsewhere (20). The biopsy samples were placed in hypotonic wash buffer and submitted for analysis. Embryos were vitrified after the biopsies. Two to nine cells were analyzed by PGS platforms. Biopsied embryos received a genetic interpretation of euploid, aneuploid, or nonconcurrent group, which included mosaics, microdeletions, and unamplified samples.

**Cryopreservation and rewarming techniques.** The cryopreservation and rewarming technique has been described previously elsewhere (19). After the embryos had been rewarmed, their embryo survival was determined according to the appearance of the blastomeres and zona pellucida, and the ability of the blastocoel to re-expand. Degenerated embryos were cataloged as nonsurviving.

**Embryo transfer.** Embryo transfers were performed under a synthetically prepared endometrium, as described previously