Depression, assisted reproductive technology/ in vitro fertilization and selective serotonin reuptake inhibitors

In this issue of *Fertility and Sterility*, Hernandez-Nieto et al. (1) present reassuring data suggesting that in vitro fertilization (IVF) patients exposed to selective serotonin reuptake inhibitors (SSRIs) in vivo are not susceptible to an increased rate of embryo aneuploidy, and that IVF outcomes of patients exposed to SSRIs do not differ from non-exposed patients (1). This reassuring publication is pertinent for many (5%-50%) of the infertile patients undergoing assisted reproductive technology (ART)/IVF, reporting anxiety and depression, many of them need medications, such as SSRI (1). Previous publications have suggested that the serotoninergic, 5-hydroxytryptamine (5-HT), transport system is expressed in the zygote and blastocyst, may regulate oocyte spawning and meiotic maturation and mammalian embryogenesis, and may either benefit or inhibit mouse blastocysts development, at different levels of exposure. Furthermore, in vitro exposure of human embryos to high SSRI concentrations may be lethal (1, 2). It has been reported that depressed pregnant parturients suffered preterm deliveries, with or without SSRI treatment.

Hernandez-Nieto et al. (1) have retrospectively analyzed the results of preimplantation genetic screening (PGS) for comprehensive chromosome analysis with quantitative polymerase chain reaction (qPCR) and/or next-generation sequencing based analysis, and evaluated IVF outcomes of their patients who underwent a single fresh or thawed euploid embryo transfer (ET) to evaluate the relationship between SSRI exposure and embryonic aneuploidy. Of all their patients, 6.40% were retrospectively categorized as having anxiety or depression and 62.4% of those declared using a SSRI medication at least one month before the follicular aspiration and throughout the first trimester, for those who conceived (1). The remaining 37.6% patients did not use SSRIs (no treatment, behavioral therapy, other antidepressants or benzodiazepines) (1). Four percent of the entire infertile population analyzed, were exposed to a SSRI medication (1). Of the overall 19,464 evaluated embryos, 54.2% (n=10,124) were euploid, 42.5% (n=8,282) aneuploid, and 5.40% (n=1,056) had a non-concurrent or inconclusive result. Of the 743 (3.9%) embryos from patients exposed to SSRIs, 40.5% were aneuploid, 54.2% euploid, and 5.2% had inconclusive results. Patients not exposed to SSRIs showed a 42.3% rate of aneuploidy, 51.9% euploidy, and 5.4% inconclusive results. Surprisingly, the estradiol (E2) concentrations on the trigger day were significantly higher in the non-SSRI exposed patients (mean ± SD: 2,163±1,122 pg/mL vs. 1,971±1,061 pg/mL; $P=.03$), and the basal anti-müllerian hormone (AMH) levels were significantly different between the two groups (3.73 ng/mL vs. 2.7 ng/mL; $P<.005$) (1). Nevertheless, the IVF outcomes: implantation rate, clinical pregnancy, miscarriage, and multiple gestation rates, were comparable between the two groups (1). The authors declare that exposure to SSRIs, before and/or during IVF treatment do not significantly modify outcomes (1). They may be right. However, to unequivocally state this conclusion a more detailed comparison between groups needs to be done. Whereas the "control" group included patients with anxiety and depression who received either no treatment, or behavioral therapy, other antidepressants, or benzodiazepines, there is a theoretical possibility that those patients exposed to other antidepressant medications, or benzodiazepins, might have had higher aneuploidy rates and inferior IVF/ART outcomes than the group not receiving any medication, or vice versa. Thus, combining the results of all the different subgroups may possibly sum up with results not different from the SSRI group, whereas some specific subgroups may have significantly different aneuploidy rates and/or outcomes.

As the authors correctly state, previous publications reached different and debatable conclusions regarding the effect of SSRI exposure on reproduction (1). Exposure to SSRIs in late gestation may lead to premature delivery and various clinical sequelae in as much as 30% of the neonates, such as neurobehavioral, respiratory, gastrointestinal, and somatic symptoms (3). Among the respiratory sequelae of intrauterine exposure to SSRIs, neonatal persistent pulmonary hypertension syndrome is a severe side effect (3). Such a causal association has been demonstrated in rodents where fluoxetine administration to pregnant rats induced fetal pulmonary hypertension (3). Therefore, even if SSRIs are shown by prospective studies not to affect aneuploidy rate in early gestation, their safety throughout pregnancy is far from being demonstrated.

The different E2 concentrations on the trigger day between the two groups ($P=.03$) and different AMH levels ($P<.005$) (1), may have possible implications on egg quality and pregnancy outcome (4). Indeed, high E2 concentrations in the late follicular phase of IVF cycles correlated with high E2 levels in the generated gestations at 4 and 8 weeks of pregnancy and with higher rates of small for gestational age and low birth weight neonates vs. spontaneous pregnancies or those generated by ET of thawed embryos, with significantly lower, physiological E2 levels (4). Baart et al. (5) have shown that milder controlled ovarian stimulation (COS) for IVF reduced aneuploidy in the human preimplantation embryos. These investigators have shown in a convincing PGS experiment that the mild ovarian stimulation generating a lower oocyte yield, and associated with lower E2 compared to the conventional IVF, was associated with a decrease in the proportion of aneuploid embryos (4, 5). The number of euploid embryos was identical regardless of whether eight embryos were generated, after conventional COS, or only four embryos, after mild COS (5). Others have also shown that mild COS generated high-quality embryos and pregnancy rate

comparable to those following conventional ovarian stimulation (4).

The significantly lower AMH levels in the SSRI treated patients (mean±SD: 2.72±2.6 ng/mL vs. 3.7±4.3 ng/mL; $P<.005$) (1), may possibly explain the tendency toward a higher early pregnancy loss rate, (18.5% vs. 11.49%, respectively; $P=.08$). Whereas there were only 97 patients in the SSRI group versus more than two thousand patients in the non-homogenous "control" group, one may speculate that future prospective comparative studies of similar sized and homogenous control groups may generate more solid and robust data. Indeed, the authors themselves declare, "due to the small sample size found in the sub analysis, specifically in the SSRIs exposed group, the study was limited in its ability to detect small and/or significant differences in patient cycle outcome(s)" (1). They correctly suggest that further investigation and randomized clinical trials with adequate power and long-term follow-up should be performed to find more accurate information about the effects of these medications on human embryo development in vivo, IVF outcomes, fetal and newborn health and long-term development outcomes.

Zeev Blumenfeld, M.D.
Reproductive Endocrinology, OB/GYN, Technion-Rappaport Faculty of Medicine, Haifa, Israel

http://dx.doi.org/10.1016/j.fertnstert.2017.09.012

You can discuss this article with its authors and with other ASRM members at
https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/20256-24997

REFERENCES

1. Hernandez-Nieto C, Lee J, Nazem T, Gounko D, Copperman A, Sandler B. Embryo aneuploidy is not impacted by selective serotonin reuptake inhibitor exposure. Fertil Steril 2017;108:973–9.
2. Kaihola H, Yaldir FG, Hreinsson J, Hörnaeus K, Bergquist J, Olivier JD, et al. Effects of fluoxetine on human embryo development. Front Cell Neurosci 2016;10:160.
3. Belik J. Fetal and neonatal effects of maternal drug treatment for depression. Semin Perinatol 2008;32:350–4.
4. Blumenfeld Z. Why more is less and less is more when it comes to ovarian stimulation. J Assist Reprod Genet 2015;32:1713–9.
5. Baart EB, Martini E, Eijkemans MJ, Van Opstal D, Beckers NG, Verhoeff A, et al. Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial. Hum Reprod 2007;22:980–8.