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 μM 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 μM 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 μs 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

elsewhere (19). The patients were prepared with estradiol (Estrace; Teva Pharmaceuticals), 2 mg twice daily for 1 week, then 2 mg three times daily, then their endometrial thickness was assessed ultrasonographically until a thickness of ≥7 mm was documented. Afterward, 50 mg of progesterone in oil was administered intramuscularly each day (progesterone injection; Watson Pharma). Thawing and transferring of the embryo was performed after 5 days of progesterone supplementation. Single-euploid embryos were selected for each transfer.

Study Groups

Main analysis. The main analysis included IVF cycles programmed for trophectoderm biopsy and PGS analysis, which had ≥1 embryo biopsied. Single gene disorder cases were excluded, and canceled or withdrawn cycles and egg donor recipient cycles also were excluded from the analysis. The embryos were segregated into two cohorts according to their exposure to SSRIs. After the PGS results had been obtained, they were classified in three categories for analysis: euploid embryos, aneuploid embryos and inconclusive reported embryos. Rebiopsied embryos were excluded from the analysis.

Subanalysis. The subanalysis for IVF outcomes included all thawed single-euploid ET cycles under a synthetically prepared endometrium performed between January 2012 and March 2017. The cohorts were defined by exposure to SSRIs, as mentioned in the main analysis.

Outcome Measures

The primary outcome of the study was to evaluate the relationship between SSRI exposure and embryonic aneuploidy. The influence of maternal age, body mass index (BMI), antimüllerian hormone levels (AMH), number of oocytes retrieved, stimulation type, total gonadotropin dose used during COH, primary diagnosis (uterine factor, diminished ovarian reserve, anovulation, hypothalamic amenorrhea, tubal factor, male factor, or endometriosis) was also determined.

Secondary outcomes of the study included implantation rate, defined as the ratio of positive pregnancy test (β-hCG > 5 mIU/mL) over the number of embryos transferred; and clinical pregnancy rate, defined as the ratio of the number of gestational sacs (determined by ultrasound at 9 days after a positive pregnancy test) to the number of transferred embryos. A multiple pregnancy was defined as two positive fetal poles with positive heart rates after a monozygotic splitting. Early pregnancy loss was defined as a loss after a positive pregnancy test and/or detectable gestational sacs.

Statistical Methods

The statistical analyses were performed using SAS version 9.4 (SAS institute Inc.). Descriptive data were compared by unpaired two-sided Student's *t*-test, where $P<.05$ was considered statistically significant. The results were expressed as mean and standard deviation with 95% confidence intervals (CI).

A univariate logistic regression analysis was performed to identify the candidate factors that were associated with the odds of aneuploidy, and the variables included were age, BMI, AMH, cumulative dose of gonadotropins, peak estradiol at surge, number of oocytes retrieved, stimulation type, primary diagnosis, and number of embryos biopsied. A logistic regression fit with generalized estimating equations was used to model the relationship between the odds of aneuploidy and the exposure to SSRIs, while accounting for a within-patient correlation of responses. All the odds ratios were adjusted by controlling for the previously mentioned variables. The odds of aneuploidy for individual patients were assumed to be equally correlated across the cycles; for this purpose we used an exchangeable working correlation structure. Odds ratio (OR) with 95% confidence interval (CI) and corresponding *P* values are presented.

For the subanalysis, hypothesis testing was performed using two-tailed Student's *t*-test at the alpha level of statistical significance at 0.05. The distribution between outcomes was assessed by chi-square test or Fisher's exact test, when appropriate. $P<.05$ was considered statistically significant. The Clopper-Pearson interval was used to calculate binomial CI for the reported proportions.

Power Analysis

For the main analysis a sample size of 392 embryos was calculated as necessary for each group to have an 80% power to detect a difference of 10% in aneuploid proportion among groups, with an alpha level = 0.05. A sample size of 329 ETs for each group (exposure vs. control) was calculated to have an 80% power to detect a 10% difference in clinical pregnancy rate with an alpha level = 0.05. And a sample size of 294 ETs for each group was calculated as being necessary to find a 10% difference in implantation rates among cohorts, with a 80% power at an alpha level = 0.05. And a sample size of 301 transfers per group was calculated as being necessary to have an 80% power to detect a 10% difference in loss rates at an alpha =0.05 between cohorts.

Regulatory Approval

This retrospective study was approved by the Western Institutional Review Board, Inc. Patient information was anonymized and deidentified before analysis.

RESULTS

Main Analysis

Between January 2012 and June 2017, a total of 7,722 cycles with planned genetic screening were analyzed. A total of 4,355 cycles met the inclusion criteria (56.39%), underwent COH, and had ≥1 blastocysts at biopsy. Canceled or withdrawn cycles, cycles without any embryos available for biopsy or rebiopsied embryos, and single gene disorder cases were excluded. Of all the patients, 282 (6.40%) were detected to have a diagnosis of anxiety or depression, with 176 (62.4%) confirmed as using a SSRI. The remaining 106 (37.6%) patients used other treatment types (behavioral therapy, other antidepressants or benzodiazepines, or no treatment). Of the

TABLE 1

Demographic characteristics and embryology data of exposed and unexposed patients.

Characteristic	SSRI exposure: No (n = 4,179)	Yes (n = 176)	*P* value
Age, y	37.0 (4.4)	37.0 (4.7)	.25
BMI, kg/m^2	23.6 (4.3)	24.3 (4.5)	.40
AMH, ng/mL	2.9 (3.6)	2.71 (2.8)	.56
BAFC	11.2 (6.1)	10.6 (5.7)	.23
FSH, IU/mL	6.2 (3.3)	6.9 (5.8)	.16
Peak E_2, pg/ml	2,163 (1,122)	1,971 (1,061)	.03*
Cumulative GND dose, IU	3,845 (1,330)	3,869 (1,384)	NS
Eggs retrieved	14.3 (8.9)	13.6 (8.1)	.27
Maturity, %	92.1	92.1	NS
Fertilization, %	63.44	63.59	.37
Total cleavage stage embryos	7.4 (6.3)	7.6 (5.6)	NS
Blastulation (blasts/eggs retrieved), %	39.74	39.44	NS
Total blastocysts	6.51 (5.0)	6.2 (4.4)	.36
Biopsied blastocysts	4.48 (3.7)	4.22 (3.4)	.35
Euploid embryos (n = 10,124), n (%)	9,721 (51.9)	403 (54.2)	.85
Aneuploid embryos (n = 8,282), n (%)	7,981 (42.3)	301 (40.5)	.11
Other results (n = 1,056), n (%)	1,017 (5.4)	39 (5.2)	.71

Note: Data presented as mean ± standard deviation, unless stated otherwise. AMH = antimüllerian hormone; BAFC = basal antral follicle count; BMI = body mass index; E_2 = estradiol; FSH = follicle-stimulating hormone; GND = gonadotropin; SSRI = selective serotonin reuptake inhibitor.
* Statistical significance, $P < .05$.

Hernandez-Nieto. SSRI exposure and embryo aneuploidy. Fertil Steril 2017.

TABLE 2

Demographic and in vitro fertilization cycle characteristics of unexposed and exposed patients at embryo transfer.

Characteristic	SSRI exposure: No (n = 2,035)	Yes (n = 97)	*P* value
Age, y	36.1 (3.9)	36.6 (3.6)	.16
BMI, kg/m^2	23.3 (4.1)	24.1 (4.5)	.07
AMH, ng/mL	3.7 (4.3)	2.72 (2.6)	< .005*
BAFC	10.1 (7.4)	9.0 (6.5)	.16
FSH, IU/mL	6.3 (3.1)	6.2 (3.7)	.96
Surge E_2, pg/ml	2,338 (2,438)	2,111 (1,870)	.41
Endometrial thickness at ET, mm	9.1 (2.0)	8.9 (1.5)	.16
Endometrial pattern at ET, mm	2	2	.19

Note: Data presented as mean ± standard deviation, unless specified otherwise. AMH = antimüllerian hormone; BAFC = basal antral follicle count; BMI = body mass index; E_2 = estradiol; ET = embryo transfer; FSH = follicle-stimulating hormone; SSRI = selective serotonin reuptake inhibitor.
* Statistical significance, $P < .05$.

Hernandez-Nieto. SSRI exposure and embryo aneuploidy. Fertil Steril 2017.

entire infertile population analyzed, 176 (4.04%) patients were exposed to a SSRI medication.

Of the included study cycles, a total of 19,464 embryos with trophectoderm biopsy and comprehensive chromosome analysis were evaluated. The rate of euploid embryos was 54.2% (n = 10,124), and the rate of aneuploidy embryos was 42.5% (n = 8,282). The remaining 5.40% (n = 1,056) of the study's entire cohort had a nonconcurrent or inconclusive result.

From the patients who were exposed to SSRI before and/or during stimulation, 743 (3.94%) embryos developed. The patients exposed to SSRI had a 40.5% rate of aneuploidy (n = 301), 54.2% rate of euploidy (n = 403), and 5.2% other results (n = 39). Patients not exposed to SSRIs showed a 42.3% rate of aneuploidy (n = 7,981), 51.9% rate of euploidy (n = 9,721), and 5.4% other results (n = 1,017). The demographic and IVF cycle characteristics of cycles analyzed are listed on Table 1.

A statistically significant difference was found in the estradiol levels on the day of the surge among SSRI-exposed and unexposed groups: 2,163 (±1,122 SD) versus 1,971 (±1,061 SD), respectively (P=.03). No statistically significant differences were found between the SSRI-exposed and unexposed patients' age, BMI, AMH level, basal antral follicle count, day-3 follicle-stimulating hormone level, cumulative gonadotropin doses, number of eggs retrieved, egg maturity rate, fertilization rate, total cleavage rate, or total blastocysts or cryopreserved blastocyst counts.

After controlling for age, BMI, AMH, cumulative dose of gonadotropins, peak estradiol at surge, number of oocytes retrieved, stimulation type, primary diagnosis, and number of embryos biopsied, there was no statistically significant association between a patient's exposure to SSRIs and the odds of having embryo aneuploidy (adjusted OR 0.04; 95% CI, −0.04–0.09; P=.14).

Subanalysis

The subanalysis included 2,132 thawed SET cycles, 4.7% (n = 97) for which the patients had confirmed SSRI exposure before and/or during treatment; the remaining 95.3% (n = 2,035) patients had no SSRI exposure. The demographic and IVF cycle characteristics of populations are shown in Table 2. The baseline AMH difference was statistically significant between the cohorts (3.73 vs. 2.7, P<.005); no other differences were found between the groups (see Table 2). As shown in Table 3, when we analyzed the IVF outcomes, we observed no differences among the cohorts 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).

DISCUSSION

In the modern era of ART advancement, PGS has been shown to be a superior method for selecting the best embryo before transfer. Through PGS for ploidy or single gene disorders, we can avoid the inheritance of certain diseases while giving greater advantage to patients by decreasing multiple pregnancy rates and improving IVF efficiency (21–25). As embryonic aneuploidy is recognized as one of the major drivers of reproductive failure (26), the theorized adverse

TABLE 3

Clinical outcomes of selective serotonin reuptake inhibitor exposed patients versus unexposed using single-embryo model.

	SSRI exposure			
Outcome rate	No (n = 2,035)	Yes (n = 97)	*P* value	OR (95% CI)
Implantation	1,451 (71.3)	68 (70.1)	.80	0.60 (0.60–1.47)
Clinical pregnancy	1,186 (58.2)	58 (59.7)	.76	0.70 (0.70–1.61)
Early pregnancy loss	234 (11.49)	18 (18.5)	.08	1.54 (0.94–2.54)
Multiple pregnancy	14 (0.6)	0	.09	0.7 (0.02–7.32)

Note: Data presented as n (%), unless specified otherwise. CI = confidence interval; OR = odds ratio; SSRI = selective serotonin reuptake inhibitor.

Hernandez-Nieto. SSRI exposure and embryo aneuploidy. Fertil Steril 2017.

effects of 5-HT concentration modifications in the oocyte and developing embryo in vivo via SSRIs were not demonstrated in this study. The study's results suggest embryo ploidy is not adversely influenced by the patient's exposure to SSRI medication. Additionally, IVF outcomes are not statistically significant modified by exposure to this family of antidepressants, even when exposed before and/or during IVF treatment.

The prevalence of anxiety and/or depression disorders in this study's population was found to be 6.40%. As the national range for depressive disorders varies from 11% to 54% (2, 27), the low prevalence within this study may be explained by our inability to obtain the patients' comprehensive past mental health history or by underreporting by the patients at initial consultation (28). It is interesting that it has been observed that <7% of couples with an infertility diagnosis consult a psychiatric specialist to navigate the disease's emotional burden (29, 30). Despite the availability of other interventions, a pharmacotherapeutic approach is used by 4% to 11% of women with infertility (31), a figure that was corroborated by our study's population: 4.04% of all patients treated at the study's clinic were exposed some type of SSRI.

The effect of SSRI exposure between matched populations has been lightly debated in the field of reproduction medicine. Similar to this study, Klock et al. (30) and Serafini et al. (32), found the number of oocytes retrieved, mature oocytes, fertilization rate, and embryo development and cryopreservation rates were similar among patients exposed to SSRI and patients unexposed. The only exception in other published research has been the high levels of estradiol at the surge found in patients not exposed to SSRIs (2,163 ±1,122 vs. 1,971 ± 1,061; $P \leq .03$). This association between higher estradiol levels during the stimulation in the unexposed patients may have been due to the difference in total patients analyzed and heterogeneity of the control group.

It has been suspected that 5-HT participates in the signaling pathways of oocyte meiotic maturation, embryogenesis, and transduction pathways of cellular proliferation (9,11–16). Our findings suggest that embryo development and chromosome segregation in vivo are not affected by the exposure to SSRIs during IVF treatment, especially as there was no effect or association in the proportion of embryo aneuploidy, euploidy, and/or other results (such as nonconcurrent reports) for the patients exposed to SSRIs. The logistic regression controlling for possible cofounders and effect modifiers found no statistically significant association between SSRI exposure and the increase in aneuploid proportion of embryos (OR 0.04, 95% CI, −0.04–0.09; $P=.14$).

A pilot study published by Klock et al. (30) analyzed 25 patients exposed to SSRIs and compared their IVF outcomes with 50 control patients. No differences in ongoing pregnancy rates (40% in exposed vs. 51% in unexposed) or loss rates (4% in exposed vs. 12% in unexposed) were observed. One caveat of that study was the use of mixed and untested day-3 embryos and blastocysts during the fresh IVF cycles. Our subanalysis addresses that study's design confounders by capitalizing on a single, euploid ET on a synthetic prepared endometrium model to control for embryonic and implantation factors. We found no differences in the rates of implantation (71.3% vs. 70.1%; OR 0.60; 95% CI, 0.60–1.47; $P=.80$), clinical pregnancy (58.2% vs. 59.7%; OR 0.70; 95% CI, 0.70–1.61; $P=.76$), loss (18.5% vs. 11.49%; OR 1.54; 95% CI, 0.94–2.54; $P=.08$), or multiple pregnancy (0.6% vs. 0%; OR 0.7; 95% CI, 0.02–7.32; $P=.09$) when comparing the SSRI exposure and no exposure cohorts. The difference in early pregnancy loss rate of this study's analysis did not reach statistical significance, but the difference in overall percentage could point toward a slight clinical trend. However, it is commonly understood that patients with infertility are at increased risk of miscarriage (3).

In spite of our best efforts to avoid biases in the study, some limitations and shortcomings do exist. The retrospective nature of the study increased the chances of a potential selection bias. The study was not limited to good- or normal-response patients, so it may have been biased in its isolation of patients who could develop high-quality blastocysts despite the COH response or protocol used. However, the statistical analyses controlled for patient age, BMI, ovarian reserve markers, and the other clinical variables of importance. Another weakness of the study includes the variety of SSRIs administered to the study's population: escitalopram (n = 75, 42.6%), sertraline (n = 64, 36.3%), fluoxetine (n = 29, 16.4%), paroxetine (n = 7, 3.9%), and citalopram (n = 1, 0.56%). It is well known that there is variability among SSRIs in the potency of 5-HT1A blockade; presently we do not know whether this impacts the amount of exposure in vivo. Also, the SSRI dosages amounts were not universal and were not properly recorded or analyzed due to the self-reporting nature of data collection. Currently there is no universal accepted dose or standard for SSRIs during ART. Furthermore, the study was unable to calculate the 5-HT concentrations in oocytes and embryos during in vivo development.

Finally, the observational nature of this study did not allow for a comprehensive assessment of the impact on treatment of the range of depression or anxiety disorders and their potential severities. Because of the diagnostic variability, patient treatments were categorized by the severity of their psychiatric disorders. A heterogeneity of treatment for depression or anxiety was found throughout the study population. When we attempted further segregation of the populations based on

types of depression, or anxiety treatments using behavioral therapy, benzodiazepines, or multiple treatment combinations, no statistically significant differences were found although the addition of such subdivisions diminished the statistical power of the study with regard to multicollinearity within the model.

There are many benefits to this study. To our knowledge, no reported study has analyzed the influence of patient exposure to SSRIs on embryo developmental and chromosomal status. Another strength is the methodological design; a statistical regression using a generalized estimating equation model allowed us to assess the known and unknown possible correlations between the variables included in the model over the whole populations analyzed, accounting for the same patient appearing multiple times on different cycles on the same database.

This study used recent, clinically validated PGS techniques to assess the rates of embryonic ploidy (33–36). PGS of trophectoderm cells involves the analysis of only a small fraction of the cells extracted of the whole embryo, which may underreport the real incidence of embryo mosaicism or microdeletions. The major strength of the study's subanalysis includes the use of the SET model, which enabled us to avoid potential embryonic factors and allowed for a synthetically prepared endometrium, thus giving our study more ability to monitor the endometrial implantation window. Additionally, the SET model avoids encountering high concentrations of steroidal hormones in the endometrial cavity, a factor that has been demonstrated to modify and affect embryo implantation (37–41).

Further, the study was appropriately powered and included a large cohort of embryos to detect statistically significant differences in the blastulation and aneuploidy rates. A large number of SET cycles added to the strength of the study's statistics and enabled us to appropriately detect substantial differences between the outcomes and parameters analyzed. However, due to the small sample size found in the subanalysis, specifically in the SSRIs exposed group, the study was limited in its ability to detect small and/or statistically significant differences in patient cycle outcome(s).

Patients should be informed that there are potential risks to baby and mother health associated with the use SSRIs with IVF. The potential risks of untreated depression or anxiety before IVF or during pregnancy also should not be ignored. If these risks outweigh the benefit of not taking any medications, antidepressant treatment should be used to improve life quality in our patients. Patients exposed to SSRIs during pregnancy have been theorized to be prone to malformations, neurodevelopmental disorders, behavioral disorders, and morbidity such as preterm birth, miscarriage, neonatal prolonged QT syndrome, preeclampsia, or pulmonary hypertension syndrome in newborns (42–47). Conversely, maternal depression and/or anxiety has been associated with birth and neurodevelopmental problems, regardless of treatment, suggesting that adverse antidepressant associations could be erroneously attributable to SSRI exposure (48–50).

To date no randomized clinical trials have been able to test the safety and efficacy of antidepressants during a women's pregnancy journey (51). Further investigation and randomized clinical trials with adequate power should be performed to find more accurate information about the effects of these medications on human embryo development in vivo, on IVF outcomes, on fetal and newborn health, and on long-term development outcomes. Long-term follow-up of infertile patients with anxiety and/or depression and cautious follow up of their progeny is needed for clinicians to recognize the true impact of SSRIs on offspring development.

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