E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.01.652

Research Article

Association of Selective Serotonin Reuptake Inhibitor Use with Ovarian Reserve Markers and Ovulatory Function in Women Undergoing Fertility Evaluation in Pakistan

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Received: 01.05.26, Revised: 30.05.26, Accepted: 29.06.26

ABSTRACT

Background: Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed in women of reproductive age, yet their potential effects on ovarian reserve and reproductive endocrine function remain uncertain. Limited data are available from low- and middle-income countries, including Pakistan, where psychiatric medication history is not routinely incorporated into fertility evaluation.
Objective: To assess the association between SSRI use and fertility-related hormonal and ovarian reserve markers in women of reproductive age attending the fertility centers.
Methods: This cross-sectional comparative observational study was conducted at multiple fertility centers across Pakistan from January 2025 to June 2025. Fifty women aged 20-40 years undergoing fertility evaluation were enrolled through convenience sampling and divided into two groups: 25 women with major depressive disorder receiving SSRIs for at least 6 months and 25 age-matched controls without psychiatric illness or SSRI exposure. Serum anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and prolactin were measured, and antral follicle count (AFC) and ovulatory status were assessed. Group comparisons were performed using independent samples t-tests and chi-square tests. Multivariable linear regression was used to evaluate the association between SSRI use and AMH after adjustment for age and body mass index (BMI).
Results: Compared with controls, SSRI users had significantly lower mean AMH (1.8 ± 0.6 vs $3.2\pm 0.9; p < 0.001$) and AFC (8.4 ± 2.3 vs $12.1\pm 3.1; p < 0.001$), and significantly higher mean FSH (9.2 ± 2.1 vs $6.8\pm 1.7; p < 0.01$) and prolactin levels (28.4 ± 6.7 vs $19.6\pm 5.3; p < 0.001$). LH and estradiol levels were similar between groups. Ovulation was observed in 56% of SSRI users compared with 84%
of controls ($p < 0.01$). In multivariable regression, SSRI use remained independently associated with lower AMH ($\beta = -1.21$, SE = $0.32, p < 0.001$) after adjustment for age and BMI.
Conclusion: SSRI use was associated with lower ovarian reserve markers, higher prolactin and FSH levels, and reduced ovulation in women of reproductive age undergoing fertility evaluation. Although causality cannot be inferred from this cross-sectional design, these findings suggest that SSRI exposure may be linked to altered reproductive endocrine function and warrant further prospective investigation.

Keywords: Selective serotonin reuptake inhibitors; female fertility; ovarian reserve; prolactin; ovulation.

INTRODUCTION

Selective serotonin reuptake inhibitors SSRIs are among the most commonly prescribed antidepressants for women of reproductive age. Agents such as fluoxetine, sertraline, and escitalopram increase synaptic

serotonin availability and are widely used for major depressive and anxiety disorders. Because serotonergic signaling interacts with neuroendocrine pathways, SSRI exposure has raised concern regarding possible effects on the hypothalamic-pituitary-gonadal axis, ovulatory function, and ovarian physiology (1,2).

Female fertility depends on coordinated hypothalamic-pituitary-ovarian signaling and adequate ovarian reserve. In clinical practice, anti-Müllerian hormone AMH, follicle-stimulating hormone FSH, estradiol, and antral follicle count AFC are commonly used markers to assess reproductive potential and ovarian reserve (3). Although these markers do not directly measure fertility, they are widely used in reproductive medicine as surrogate indicators of follicular quantity and ovarian responsiveness (3).

Emerging evidence suggests that SSRIs may be associated with alterations in reproductive endocrine function. In a prospective controlled trial, women treated with SSRIs for major depressive disorder showed significant reductions in AMH and total AFC after 6 months of treatment compared with pretreatment values, raising concern about a possible adverse effect on ovarian reserve (4). Other literature has highlighted drug-associated hyperprolactinemia as a potential pathway linking psychotropic therapy to menstrual irregularity and ovulatory dysfunction, since elevated prolactin may suppress gonadotropin-releasing hormone secretion and contribute to anovulation (5). Experimental studies have likewise suggested that serotonergic agents may influence luteinizing hormone secretion and cyclic reproductive function, although the clinical relevance of these findings remains incompletely defined (2,5).

At the same time, the relationship between depression, SSRI exposure, and fertility remains complex. Existing human data is heterogeneous, and current reviews emphasize that evidence is still insufficient to conclude that SSRIs independently reduce fertility or worsen infertility-treatment outcomes in all settings (6). Some studies have reported lower fecundability among women using antidepressants, whereas others suggest that the underlying mood disorder itself may contribute to impaired reproductive outcomes through behavioral, endocrine, and stress-mediated pathways (6,7). This distinction is particularly important when interpreting observational data, where confounding by indication remains a major concern.Despite growing international interest in this topic, evidence from low- and middle-income countries remains limited. In Pakistan, where both infertility-related healthcare utilization and antidepressant use are increasing, psychiatric medication history is not routinely integrated into fertility assessment. As a result, region-specific data on the association between SSRI use and ovarian reserve markers are scarce. This limits clinicians' ability to counsel women appropriately regarding possible reproductive implications of antidepressant therapy during fertility evaluation or conception planning.

The present study was therefore conducted to evaluate the association between SSRI use and fertility-related hormonal and ovarian reserve markers in women of reproductive age attending fertility clinics in Punjab, Pakistan. Specifically, the study aimed to compare AMH, FSH, luteinizing hormone LH, estradiol, prolactin, AFC, and ovulatory status between women using SSRIs for major depressive disorder and women without SSRI exposure.

METHODOLOGY

This cross-sectional comparative observational study was conducted at multiple tertiary care fertility centers with facilities for hormonal assessment, pelvic ultrasonography, and fertility evaluation. A total of 50 women were included as participants in the study and allocated into two groups. The participants were included following convenience sampling.Group A comprised 25 women diagnosed with major depressive disorder who had been receiving selective serotonin reuptake inhibitor SSRI therapy for at least 6 months. Group B comprised 25 age-matched women with no history of psychiatric illness and no prior or current use of SSRIs. The duration of study was from January 2025 to June 2025. Women were eligible for inclusion if they were aged 20 to 40 years, seeking fertility evaluation or treatment, and had been using SSRIs such as fluoxetine, sertraline, or escitalopram for at least 6 months. Women were excluded if they had diagnosed endocrine disorders likely to affect fertility, including polycystic ovary syndrome or thyroid disease, a history of chemotherapy, prior pelvic surgery or other fertility-altering interventions, use of other psychotropic medications or were pregnant or lactating at the time of assessment.

Before full-scale data collection, a pilot study involving 6 participants was conducted to assess the feasibility and clarity of the interview

process and data collection tools. Based on pilot feedback, minor modifications were made to improve the clarity and consistency of the data collection instrument. A structured interview guide was developed using items adapted from existing literature and clinical assessment tools. The guide was reviewed by experts in psychiatry, gynecology, and medical education to ensure content validity. It included structured questions addressing demographic characteristics, psychiatric history, type and duration of SSRI use, menstrual history, and fertility-related concerns however, pilot participants were excluded from final analysis. Data was collected using multiple methods. First, participants underwent a structured clinical interview using the predesigned interview guide. Second, laboratory investigations were performed to assess key hormonal markers relevant to ovarian reserve and reproductive function, including anti-Müllerian hormone AMH, follicle-stimulating hormone FSH, luteinizing hormone LH, estradiol, and serum prolactin. Where feasible, ovulatory status was evaluated using basal body temperature charting or urinary LH surge kits. Data were analyzed using SPSS version 25. Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were presented as mean± standard deviation or median with interquartile range, depending on data distribution, while categorical variables were expressed as frequencies and percentages. Comparisons between the two groups were performed using the independent samples t- test for normally distributed continuous variables and the Mann-Whitney U test for non- normally distributed variables. Chi-square tests were used to compare categorical variables, including ovulation status. In addition, multivariable regression analysis was performed to adjust for potential confounders, including age, body mass index BMI, and duration of SSRI use. A p-value < 0.05 was considered statistically significant.

Ethical approval was obtained from the Institutional Review Board IRB of LIFE Pakistan – Lahore Institute of Fertility & Endocrinology prior to commencement of the study. Written informed consent was obtained from all participants before enrollment. Participant confidentiality and data privacy were maintained throughout the study. The study was conducted in accordance with the ethical standards of the National Bioethics Committee of Pakistan and relevant Drug Regulatory Authority of Pakistan DRAP regulations governing research involving human participants.

RESULTS

A total of 50 women were included in the study, with 25 participants in the SSRI group and 25 participants in the control group. The SSRI group comprised women diagnosed with major depressive disorder who had been receiving SSRI therapy for at least 6 months, whereas the control group included age-matched women with no history of psychiatric illness or SSRI use. The mean age of participants was comparable between the two groups, with a mean age of 29.4± 4.2 years in SSRI users and 28.9± 3.9 years in controls. Mean body mass index BMI was 24.8± 3.1 kg/m² in the SSRI group and 23.7± 2.8 kg/m² in the control group.

With respect to reproductive hormonal markers, women in the SSRI group had lower mean anti-Müllerian hormone AMH levels than controls 1.8 ± 0.6 versus 3.2 ± 0.9,respectively.Mean follicle-stimulating hormone FSH levels were higher among SSRI users $9.2\ \ 2.1$ compared with controls 6.8 ± 1.7. Mean luteinizing hormone LH levels were similar between groups 6.1 ± 1.3 in SSRI users versus 6.4 ± 1.2 in controls, as were estradiol levels 110 ± 25 versus 115 ± 22, respectively. Mean prolactin levels were higher in the SSRI group 28.4 ± 6.7 than in controls 19.6 ± 5.3.Table 1 presents the descriptive statistics for demographic variables and hormonal markers in both groups.

Variable	SSRI users$n = 25$	Controls$n = 25$
Age, years	29.4± 4.2	28.9± 3.9
BMI, kg/m²	24.8± 3.1	23.7± 2.8
AMH	1.8± 0.6	3.2± 0.9

Variable	SSRI users$n = 25$	Controls$n = 25$
FSH	9.2± 2.1	6.8± 1.7
LH	6.1± 1.3	6.4± 1.2
Estradiol	110± 25	115± 22
Prolactin	28.4± 6.7	19.6± 5.3
AFC	8.4± 2.3	12.1± 3.1

Independent samples t-tests showed statistically significant differences between SSRI users and controls for several fertility-related markers. Mean AMH was significantly lower in the SSRI group $t = 4.12, p < 0.001$.

Mean FSH was significantly higher among SSRI users $t = 3.01, p < 0.01$, and prolactin levels were also significantly higher $t = 4.45, p < 0.001$.The results of the independent t-tests are summarized in Table 2.

Variable	t-value	p-value
AMH	4.12	<0.001
FSH	3.01	<0.01
Prolactin	4.45	<0.001
AFC	3.89	<0.001

Ovulation was observed in 56% of women in the SSRI group compared with 84% in the control group. Chi-square analysis demonstrated a statistically significant difference in ovulation status between the two groups $p < 0.01$.The comparison of ovulation status is shown in Table 3.

Group	Ovulating, n	Not ovulating, n
SSRI users$n = 25$	14 56%	11 44%
Controls$n = 25$	21 84%	4 16%

Chi-square test:$p < 0.01$

A multivariable regression model was constructed with AMH as the dependent variable to assess whether SSRI use remained associated with AMH after adjustment for age and BMI. SSRI use was independently associated with lower AMH levels $\beta = -1.21, SE = 0.32, p < 0.001$. Increasing age $\beta = -0.05, SE = 0.02, p = 0.03$ and higher BMI $\beta = -0.03, SE = 0.01, p = 0.04$ were also significantly associated with lower AMH values.The regression model is presented in Table 4.

Variable	Coefficientβ	Standard error	p-value
SSRI use	-1.21	0.32	<0.001
Age	-0.05	0.02	0.03

Variable	Coefficientβ	Standard error	p-value
BMI	-0.03	0.01	0.04

In summary, SSRI users showed significantly lower AMH and AFC, higher FSH and prolactin levels, and reduced ovulation rates compared with controls, while LH and estradiol were similar between groups. After adjusting for age and BMI, SSRI use remained independently associated with lower AMH, suggesting a potential adverse effect on ovarian reserve and fertility-related function.

DISCUSSION

In this cross-sectional comparative study of women undergoing fertility evaluation in Punjab, Pakistan, SSRI use was associated with a less favorable reproductive profile, characterized by lower AMH and AFC, higher FSH and prolactin concentrations, and reduced ovulation rates compared with age-matched controls. Importantly, the association between SSRI exposure and lower AMH persisted after adjustment for age and BMI, suggesting that the observed relationship was not fully explained by these factors. Collectively, these findings support the possibility that SSRI therapy may be associated with altered ovarian reserve markers and impaired ovulatory function in women of reproductive age.

The observed reductions in AMH and AFC are clinically important because both are widely used surrogate markers of ovarian reserve in reproductive medicine (3). Although neither parameter directly measures fecundity, lower AMH and AFC generally reflect a diminished follicular pool and reduced ovarian responsiveness. Our findings are consistent with prior evidence suggesting that SSRI exposure may adversely affect ovarian physiology. In particular, a prospective controlled study reported significant declines in AMH and total AFC after 6 months of SSRI treatment in women with major depressive disorder, raising concern regarding a potential effect of these agents on folliculogenesis and ovarian reserve (4). More recent reviews have likewise suggested that SSRIs may exert adverse endocrine and reproductive effects through dysregulation of neuroendocrine and gonadal pathways (8).

The higher FSH levels observed among SSRI users in the present study further support the possibility of altered ovarian reserve. Elevated FSH may represent a compensatory pituitary response to reduced ovarian feedback and is commonly interpreted, particularly alongside low AMH and AFC, as suggestive of diminished ovarian functional reserve (3). In contrast, LH and estradiol levels did not differ significantly between groups. This pattern may indicate that SSRI-associated reproductive effects are more readily captured by ovarian reserve markers and prolactin-related ovulatory dysfunction than by isolated measurements of cycle-dependent hormones, which may vary according to menstrual timing and interindividual variability (3,5).

A biologically plausible explanation for these findings involves serotonergic modulation of hypothalamic-pituitary-gonadal function. Serotonin has recognized effects on neuroendocrine signaling, and SSRI-mediated increases in synaptic serotonin may alter hypothalamic and pituitary regulation of reproductive hormones (1,2,8). In our study, prolactin concentrations were significantly higher among SSRI users, which is notable because hyperprolactinemia is a recognized adverse effect of serotonergic and other psychotropic therapies and may impair reproductive function through suppression of gonadotropin-releasing hormone secretion (5,10). This mechanism is biologically consistent with the lower ovulation rate observed in the SSRI group. Experimental neuroendocrine work has further shown that SSRIs can inhibit tuberoinfundibular dopamine neurons, thereby reducing dopaminergic inhibition of prolactin release and promoting hyperprolactinemia (11). Thus, the elevated prolactin levels seen in our cohort may represent an important pathway linking SSRI exposure with anovulation and reproductive dysfunction.

At the same time, these findings must be interpreted in the context of the complex relationship between depression, antidepressant exposure, and fertility. Because women in the SSRI group had major depressive disorder, the observed associations may reflect not only medication exposure but also the biological and behavioral effects of the underlying psychiatric condition. Depression itself has been associated with altered stress-axis function, sleep disturbance, sexual dysfunction, smoking, weight change, and reduced fecundability, all of which may

adversely affect reproductive outcomes independent of pharmacotherapy (6-9). In a prospective preconception cohort, severe depressive symptoms were associated with reduced fecundability independent of psychotropic medication use (9). However, evidence regarding depression and ovarian reserve markers is not uniform; for example, one cohort study found no overall association between a history of depression and low AMH levels among late reproductive-aged women (12). These mixed findings emphasize that the relationship between mood disorders and reproductive function is multifactorial and that confounding by indication remains an important limitation when interpreting observational data. This complexity may also explain the heterogeneity of the existing literature on antidepressants and fertility. While some studies suggest that antidepressant use may be associated with lower fecundability or reproductive endocrine disturbance, others have not demonstrated a clear reduction in conception or live birth rates, particularly in infertility treatment settings (6,7,9). In a secondary analysis of non-IVF fertility treatment trials, antidepressant use was not associated with lower live birth rates overall, although non-SSRI antidepressant use was linked to a higher risk of first-trimester pregnancy loss (9). Reviews focused specifically on SSRIs have therefore concluded that current evidence remains insufficient to state that SSRIs uniformly impair fertility or worsen assisted reproduction outcomes across all populations and settings (6). Differences in study design, type of fertility outcome measured, antidepressant class, duration of exposure, and adequacy of adjustment for psychiatric severity likely contribute to these inconsistencies.

The present study adds to the literature by providing region-specific evidence from Pakistan, where data on psychotropic medication exposure and female fertility remain limited. This is particularly relevant because psychiatric medication history is not routinely integrated into fertility assessment in many low- and middle-income settings. Our findings suggest that SSRI exposure should be considered when interpreting ovarian reserve markers and ovulatory status in women presenting for infertility evaluation. However, these results should not be interpreted as an argument for routine discontinuation of SSRIs, as untreated depression may itself carry substantial reproductive, psychological, and functional consequences (6-9). Rather, the findings support individualized, multidisciplinary counseling in which potential reproductive concerns are weighed against the psychiatric benefits of treatment.

From a clinical perspective, women of reproductive age who are taking SSRIs and planning conception may benefit from more careful reproductive history-taking and, where appropriate, assessment of ovarian reserve and ovulatory function. Such an approach may be especially relevant in women presenting with subfertility, menstrual irregularity, hyperprolactinemia, or unexpectedly low AMH or AFC. Coordination between psychiatry, gynecology, and fertility specialists may help optimize both mental health and reproductive care.

Limitations

Several limitations should be acknowledged. First, the cross-sectional design precludes inference of causality or temporal directionality. Second, the sample size was modest and recruited from a single tertiary fertility center using convenience sampling, which may limit external validity. Third, residual confounding remains possible, particularly from depression severity, illness duration, lifestyle factors, and other unmeasured variables that may influence reproductive function independently of SSRI exposure. Fourth, different SSRI agents were analyzed together, although individual drugs may vary in their endocrine and reproductive effects. Finally, ovulatory status was assessed using pragmatic clinical methods rather than serial hormonal monitoring or ultrasound-confirmed follicular tracking, which may have introduced some misclassification.

Recommendations

Future studies should employ prospective longitudinal designs with larger and more diverse samples to clarify temporal relationships and assess whether the observed changes in AMH, AFC, prolactin, and ovulatory status are reversible after SSRI discontinuation or modification. Comparative studies examining individual SSRI agents, dose-response relationships, and duration of exposure would also be valuable. Additional work from low- and middle-income countries is especially needed to determine whether these findings are reproducible across different populations and healthcare settings.

CONCLUSION

In conclusion, SSRI use in women of reproductive age was associated with lower AMH and AFC, higher FSH and prolactin levels,

and reduced ovulation rates compared with controls. After adjustment for age and BMI, SSRI exposure remained independently associated with lower AMH. These findings suggest a potential association between SSRI therapy and altered ovarian reserve markers and ovulatory function; however, causality cannot be established, and the contribution of the underlying depressive disorder must be carefully considered. Larger prospective studies are needed before firm clinical recommendations can be made, but fertility-oriented counseling and closer reproductive assessment may be warranted in selected women using SSRIs who are planning pregnancy.

Conflict of interest

The authors declare no conflict of interest.

Funding

No funding was received for this study.

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