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Comparison of the groups treated with mirtazapine and selective serotonin reuptake inhibitors with respect to birth outcomes and severity of psychiatric disorder

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ABSTRACT

Objective: The literature provides very limited information on mirtazapine usage in the pregnancy period. The groups including pregnant women who used SSRI or mirtazapine as a single treatment, SSRI-mirtazapine combination treatment and unmedicated groups were compared with respect to illness severity and birth outcomes.

Method: The study sample included 120 pregnant women; 40 women with SSRI usage, 16 women with mirtazapine usage, 18 women with combined SSRI- mirtazapine usage, 23 women with unmedicated psychiatric disorder and who elected not to take medication during their pregnancy or discontinued antidepressants by themselves, and 23 healthy control women.

Results: No difference was obtained with regard to the gestation week of birth, birth weight, the duration of stay in the neonatal care unit among the SSRI, mirtazapine, SSRI-mirtazapine combination, unmedicated patient and control groups. The likelihood of a new diagnosis was highest in the mirtazapine group. The majority of pregnant women whose psychiatric disorders were more severe and more relapsed used SSRI-mirtazapine combination treatment.

Conclusion: No difference was observed between the SSRI and mirtazapine usage in the pregnancy period with regard to the birth outcomes. Similar birth outcomes could present clinicians with the option of prescribing mirtazapine as a safe alternative to SSRI in the treatment of antenatal psychiatric patients.

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SSRI; mirtazapine; birth week; birth weight; birth outcomes; illness severity

Introduction

Studies in perinatal psychiatry report that the percentage of anxiety disorders in pregnant women is 4%–39% [1], whereas that of depressive disorders is 18% [2] in. The use of antidepressants during pregnancy is on the increase worldwide. The study suggested that although psychotherapy has been the first treatment option for mild to moderate psychiatric disorder, 70% of patients are primarily treated with antidepressants [3]. The studies also revealed an increase in the prevalence of antidepressant exposure from 0.2% to 3.2% between 1997 and 2010 in Denmark [4] and from 0.8% to 2.1% between 1999 and 2014 in the Netherlands [5]. The rate of use of SSRI (Serotonin Reuptake Inhibitors) in all antidepressants during pregnancy was reported as 63% to 85% [6].

Prenatal mental illnesses have been associated with adverse effects on pregnancy and poor neonatal outcomes [7,8]. The research reported that a 10%–15% risk of negative outcomes in newborns could be attributable to prenatal depression and anxiety [9].

There are studies investigating the short and long term effects of antidepressant medication during pregnancy. However, the accuracy of the knowledge obtained from these studies is debatable due to the lack of randomized trials on antenatal antidepressant exposure. On the other hand, population-based registry and epidemiological studies recorded the SSRI usage in pregnancy, with most of them focusing on the teratogenic effects of SSRIs. Epidemiological studies provide strong evidence with respect to a large sample size, but they still have certain limitations. Pregnant women using pharmacological medication could be experiencing more severe psychiatric disorders than untreated pregnant women. Thus, the effects of psychiatric medication cannot be excluded from the effects of more severe psychiatric disorders. Additionally, these studies include the risk of misclassified exposure, as the data has been obtained from prescription information [6]. These studies exclude the information related to mental disorder characteristics, such as the severity of the mental disorder, duration and response or resistance to the treatment. Moreover,

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these studies also lack data regarding the which trimester the exposure occurred in, and the dosage of antidepressants administered. The comorbidity of medical illnesses, smoking, and environmental factors are confounding factors of these populations. A limited number of studies include detailed information related to sociodemographic information, the existence of physical health problems, the clinical course of mental disorders during pregnancy and the outcomes in the newborn.

Up to now, SSRIs have been used as the first-line option by clinicians when anxiety and depressive disorders are treated pharmacologically during pregnancy [9]. On the other hand, the guidelines are unclear in terms of selecting a first-line drug, switching antidepressants or pregnancy-specific recommendations, and no evidence-based consensus has been reached [10]. SSRIs could aggravate morning sickness by causing gastrointestinal system irritation at the initiation of the treatment. While using SSRI, it may be required to wait for a period of time until treatment response for anxiety and depression. Antihistaminic agents and benzodiazepines could be necessary adding to the treatment in patients with severe symptoms at the beginning of the treatment with SSRIs. However, at the beginning of the treatment mirtazapine may contribute to decreased nausea, decreased symptoms of anxiety and the alleviation of insomnia. The pharmacological properties of mirtazapine offer a treatment option without the need to use anxiolytic and hypnotic agents. The importance of monotherapy increases at pregnancy.

The widespread usage of SSRIs provides knowledge related to the effects of SSRIs on the developing fetus during pregnancy and on neonatal outcomes after delivery. However, there is limited information related to mirtazapine usage and its effects on pregnancy outcomes. The off label use of mirtazapine for morning sickness has been increasing gradually in pregnant women [11]. More information is needed about its use in pregnant women with psychiatric symptoms. The literature offers insufficient information about the comparison of SSRI and mirtazapine usage in pregnancy, including the clinical course of mental disorders and birth outcomes. Although two studies compared a mirtazapine and an SSRI group according to the rates of congenital malformations and birth outcomes, the data of this study was obtained from a Teratology Information Service and contained no information related with the psychiatric follow up and the characteristics of the psychiatric patient group [12,13].

This study aims to compare pregnant women groups medicated with SSRI or mirtazapine as a single treatment, combined SSRI-mirtazapine treatment, unmedicated, and healthy control groups with regard to birth outcomes. The unmedicated pregnant group was included in the study to distinguish the effect of medication. A healthy control group was included to investigate the effect of psychiatric disorders during pregnancy. We

excluded pregnant women who had other medical conditions. The severity of antenatal psychiatric disorder and smoking were included as variables that might affect the birth outcomes, and the effects of these variables on birth outcomes were controlled.

Methods

A total of 97 patient pregnant women and 23 healthy pregnant women that meet the criteria for inclusion and exclusion participated in this study.

Patient pregnant women were followed naturalistically throughout their pregnancy. The first visit of every patient included a detailed medical, psychiatric and family history of women and Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID-I) administration. The psychiatric examination, the existence of physical medical illness, the psychiatric medication, use of other medications, Clinical Global Impression (CGI) Scale scores were documented in every individual visit. After delivery, the medical records of the baby were recorded. We informed all patients and their first degree-relatives (especially partners) about the clinical status and potential benefits and risks of pharmacological treatments. The treatment choice and decisions were individualized. If the severity of the antenatal psychiatric disorder was low to moderate, alternative treatments to pharmacotherapy, including cognitive behavioral, interpersonal and supportive psychotherapeutic approach might be initiated. Furthermore, psychotherapy was utilized for pregnant women who preferred such treatment over medication. We preferred using monotherapy as a principle in the pregnancy period, especially during the first trimester. However, when the symptoms could not be treated with monotherapy, we treated psychiatric disorder with a combined option. Since the exposure of sertraline at pregnancy is not associated with malformations [14] and suitable for breastfeeding mothers, we selected sertraline as an SSRI agent if the patient reported no previous use of antidepressants. Similarly, the report recommended sertraline as a preferred initial treatment [3]. We selected mirtazapine if insomnia, loss of appetite and anxiety were manifest symptoms. Seven women used either paroxetine, escitalopram or fluoxetine as an antidepressant. These antidepressants were used due to previous benefits, the history of non-response to another antidepressant, patient's preference or being clinically stable with the medication. The Dutch Multidisciplinary guideline recommends continuing the use of antidepressants without switching to another if the patient is clinically stable [15]. We informed patients about the higher teratogenicity risks of paroxetine with respect to other SSRIs [16].

The patient participants represent all women that were followed up between December 2015 and June 2018 and who met the eligibility criteria. A total of

40 women with SSRI usage, 16 women with mirtazapine usage, 18 women with combined SSRI- mirtazapine usage, 23 women with unmedicated psychiatric disorder and who elected not to take medication during their pregnancy or discontinued antidepressants by themselves, and 23 healthy control women with no current nor previous psychiatric disorder history were recruited in the study. The healthy control participants were recruited from the first step medical unit.

The local medical Ethics Committee (2018-208) approved the study.

Inclusion criteria

The inclusion criteria involved the pregnancies in women older than 18 with live and singleton births. Multiple pregnancies encounter certain risks, including preterm birth and low birth weight (LBW) in the course of pregnancy. Thus, only singleton pregnancies were included in the study.

Exclusion criteria

The exclusion criteria were the use of medications (including antihistaminic agents, benzodiazepines, herbal medicine, antipsychotics) other than SSRI or mirtazapine for psychiatric disorder, diagnosis of psychosis or bipolar disorder, or the existence of a physical illness known to be a risk for adverse effects on the foetus for both the patient and control groups. The excluded physical illnesses were cardiovascular and pulmonary system diseases, neurological diseases, metabolic diseases, gestational hypertension and placental abnormalities including placenta previa, ablatio placenta, and maternal infections. Two women with diabetes mellitus and a history of uncontrolled blood sugar during pregnancy were excluded from the healthy control group. Also, pregnancies which ended via miscarriage, termination or stillbirth were excluded.

The clinical global Improvement scale (CGI)

The scale provides a brief and practical assessment of the clinician's view of the patient's global functioning and wellness before and after the initiation of the treatment in daily clinical practice. The scale offers an opportunity for the assessment of all psychiatric disorders. The CGI evaluates the symptom severity of the psychopathology and the progress from the initiation of the treatment [17,18].

Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID-I) SCID is a structured clinical interview form developed by Spitzer et al. to diagnose DSM-IV Axis-I disorders [19].

Birth outcomes

The antenatal or prenatal period is defined as the period during pregnancy and before partum. Preterm

birth is less than 37 completed weeks of gestation; early-term is 37 0/7 weeks of gestation through 38 6/7 weeks of gestation, term 39 0/7 weeks of gestation through 40 6/7 weeks of gestation, late-term 41 0/7 weeks of gestation through 41 6/7 weeks of gestation. An LBW is defined as a birth weight lower than 2500 g, and macrosomia is defined as a birth weight higher than 4000 g [20,21]. The information about gestational age, weight of the newborn at birth, manner of delivery and obstetric history (previous abortus or intrauterine exitus of the fetus) were obtained from hospital and medical records. The diagnosis of poor neonatal adaptation syndrome was included if it was diagnosed by a pediatrician and mentioned in the medical records.

Covariates

The important covariates were selected based on the previous literature. Demographic information, including maternal age, education level, status of smoking and consumed amount of cigarette per day was based on self-reporting.

Statistics

The psychiatric disorders from previous pregnancies, previous treatment cessation history, and previous relapse after treatment cessation were calculated for the patients with a psychiatric diagnosis before their current pregnancies. Newly diagnosed pregnant women were excluded from this comparison. The statistical analyses were carried out using SPSS version 21.0 for Windows. The Kolmogorov-Smirnov test was utilized to check for normal distribution. The categorical variables among the study groups were compared using the Chi-square test and Fisher's exact test. The Kruskal-Wallis test was used to compare the continuous variables among more than two groups. The Bonferroni correction was applied for multiple comparisons between each pair of subgroups. Statistical significances were observed in the comparison of the clinical properties of four patient groups. Six comparisons were conducted between four groups. The p value was divided by the number of comparisons. The differences were considered to be statistically significant when the p value was <0.0083 ($0.05/6$). The correlations were evaluated by the Spearman correlation test. The Cochran Mantel Haenszel test was used to detect the effect of confounding variables between the dependent variable and the independent variable. The test was run at each of 2×2 tables. The equivalent antidepressant dosages were calculated as determined at the study of Hayasaka [22].

Results

A total of 97 patient pregnant women were included in the study. No alcohol nor substance abuse during

pregnancy was reported during the whole sampling period. Four women reported a history of intrauterine exitus fetus in previous pregnancies. One woman attempted suicide with 25 sertraline pills at 22 gestational weeks of her pregnancy. This woman gave birth to a healthy newborn.

The diagnosis of four patient groups was presented in Table 1. Patients were diagnosed with depressive disorders, depressive disorders with anxious distress, panic disorders, obsessive-compulsive disorders, generalized anxiety disorders, adjustment disorders and comorbidity of these mentioned diagnoses.

Among the included pregnant women, 37% percent of the pregnancies were terminated by vaginal delivery, whereas 67% gave birth by cesarean section, which was performed primarily owing to previous deliveries occurring in the same manner. Cesarean sections were also performed due to delivery dystocia, fear of delivery, breech presentation, macrosomia, cord prolapse, patient preference, nonstress test finding of foetal distress, postmaturity, tubal ligation, intrauterine growth retardation, oligohydramnios and the medical status of the women. Twenty-two neonates were admitted to the neonatal intensive care unit (NICU) in all groups, including both patient and control groups. One neonate was admitted to the NICU for neonatal adaptation syndrome. The other reasons admission to the NICU included meconium aspiration, neonatal infection, hypoglycemia, neonatal transient tachypnea and small-for-gestational-age.

A total of 40 women used SSRI during their pregnancy. The number of pregnant women according to the treatment options were as follows: 35 were treated

with sertraline (the mean dosage was 51.07 ± 33.6 mg/per day), three with paroxetine (the mean dosage was 20 mg/per day) and two with escitalopram (the mean dosage was 15 mg/per day). The initiation time of the treatment with respect to trimester were as follows: Twelve women in the first, 24 women in the second and 4 women in the third trimester. Paroxetine use was continued by two patients on their own volition before admission. These women were exposed to paroxetine in the first trimester. The bilateral pes equinovarus was determined in the second-trimester ultrasonography screening of one fetus that was exposed to paroxetine in the first trimester.

A total of 16 women used mirtazapine during their pregnancy; six patients in the first trimester, 3 in the second and 7 in the third trimester began to use mirtazapine. The mean dosage of mirtazapine was 21.09 ± 8.75 mg/per day.

Eighteen women used the SSRI-mirtazapine combination during their pregnancies. During these pregnancies, 17 sertraline (the mean dosage was 53.12 ± 26.80 mg/per day), 1 paroxetine (at 20 mg/per day) and 1 fluoxetine (at 20 mg/per day) were used. The mean dosage of mirtazapine was 21.6 ± 11.7 mg/per day. Five pregnant women began to use the SSRI-mirtazapine combination in the first trimester, 11 women in the second, and 2 women in the third trimester.

Table 2 presents the comparison of the sociodemographic properties of the groups. No significant differences were observed among the five groups with regard to age, educational level, and smoking status.

Table 3 presents the comparison of properties and the illness severity of the groups. The rate of new

Table 1. Diagnosis of patient groups.

	SSRI exposed (N = 40)	Mirtazapine exposed (N = 16)	SSRI-mirtazapine exposed (N = 18)	Psychiatric diagnosis unmedicated (N = 23)
Depressive disorder (N = 23)	8	5	5	5
Depressive disorder with anxious distress (N = 16)	8	3	4	1
Panic disorder (N = 21)	8	5	3	5
Obsessive compulsive disorder (N = 9)	3	0	1	5
Generalised anxiety disorder (N = 8)	0	1	1	6
Adjustment disorder (N = 3)	3	0	0	0
Generalised anxiety and depressive disorder comorbidity (N = 3)	2	0	0	1
Obsessive compulsive disorder and depressive disorder comorbidity (N = 5)	2	1	2	0
Generalised anxiety disorder and obsessive compulsive disorder comorbidity (N = 1)	1	0	0	0
Panic disorder and depressive disorder comorbidity (N = 8)	5	1	2	0

Table 2. Comparison of the sociodemographic properties of the groups.

	SSRI exposed (N = 40)	Mirtazapine exposed (N = 16)	SSRI-mirtazapine exposed (N = 18)	Psychiatric diagnosis unmedicated (N = 23)	Healthy Control (N = 23)	df	χ^2	p Chi Square/ Kruskal Wallis
Age	32.52 ± 4.87	34.87 ± 5.22	32.22 ± 4.13	33.04 ± 3.05	30.73 ± 3.88	4	9.20	0.056
Education	8.85 ± 4.17	7.31 ± 4.25	9 ± 3.91	8.21 ± 4.64	9.65 ± 4.78	4	3.08	0.544
Smoking (Yes/No)	%43/%57	%43/%57	%42/%58	%19/%81	%21/%79	4	5.51	0.231
Cigarette per day	3.12 ± 6.22	3.56 ± 5.37	4.29 ± 6.62	1.38 ± 3.54	0.73 ± 2.15	4	6.87	0.143

Table 3. Comparison of properties of illness of the groups.

	SSRI exposed (N = 40)	Mirtazapine exposed (N = 16)	SSRI-mirtazapine exposed (N = 18)	Psychiatric diagnosis unmedicated (N = 23)	df	χ^2	p Chi Square/ Kruskall Wallis
Psychiatric disorder at previous pregnancy (Yes/No)	%13/%87	%37/%63	%23/%76	%33/%67	3	3.71	0.294
Psychiatric disorder duration	58.66 ± 51.78	40.12 ± 40.94	77.55 ± 56.01	64.64 ± 55.49	3	4.79	0.187
New diagnosis at current pregnancy (Yes/No)	%15/%85	%38/%62	%0/%100	%13/%87	3	10.75	0.013
Previous treatment cessation history (Yes/No)	%67/32	%77/%23	%100/%0	%80/%20	3	7.40	0.060
Previous relaps after treatment cessation (Yes/No)	%58/%42	%67/%33	%100/%0	%55/%45	3	10.80	0.013
Pregnancy week as soon as relaps	12.37 ± 8.02	13.13 ± 8.69	11.88 ± 6.46	12.52 ± 7.73	3	0.06	0.996
Pregnancy week as soon as admission to hospital	15.47 ± 7.56	17.87 ± 9.97	15.33 ± 6.92	17.35 ± 10.93	3	0.51	0.917
The time to relaps (month)	6.56 ± 8.80	6.28 ± 11.53	7.19 ± 10	6.51 ± 7.52	3	0.95	0.812
The week of treatment onset	15.37 ± 7.98	18.80 ± 11.50	16.83 ± 7.14		2	0.90	0.635
The duration of treatment at pregnancy (week)	21.70 ± 9.77	21.5 ± 11.12	20.72 ± 8.70		2	0.18	0.913
Equivalent antidepressant dosage	27.45 ± 16.91	21.09 ± 8.75	¹ EAD SSRI 27.47 ± 13.05 ² EAD mirtazapine 23.33 ± 11.47		2	1.23	¹ 0.539
					2	0.94	² 0.625
The severity of disorder as soon as admission (Borderline mentally ill/Mildly ill/Moderately ill/Markedly ill/Severely ill/The most severely ill)	%5/%0/%33/%57/%2/%2	%6/%0/%50/%44/%0/%0	%0/%0/%5/%61/%34/%0	%0/%36/%55/%9/%0/%0	15	66.24	0.001
The severity of disorder (Mild to moderate/severe)	%37/%63	%56/%44	%5/%95	%9/%91	3	36.72	0.001
Inpatient treatment(Yes/no)	%5/%95	%18/%82	%39/%61	%0/%100	6	20.12	0.003

EAD: Equivalent antidepressant dosage.

Table 4. Comparison of the birth and infant outcomes of the groups.

	SSRI exposed (N = 40)	Mirtazapine exposed (N = 16)	SSRI-mirtazapine exposed (N = 18)	Psychiatric diagnosis unmedicated (N = 23)	Healthy Control (N = 23)	df	χ^2	P Chi Square/ Kruskall Wallis
The way of labour (vaginal/surgical delivery)	%38/%62	%37/%63	%45/%55	%31/%69	%34/%66	4	0.73	0.947
The category with regard to birth weight (Normal/LBW/Macrosomia)	%85/%10/%5	%93/%7/%0	%88/%6/%6	%86/%14/%0	%86/%8/%6	8	4.11	0.847
Gestation week of the birth	38.43 ± 1.23	38.99 ± 1.37	38.35 ± 1.40	38.09 ± 2.73	38.76 ± 1.70	4	5.99	0.200
Preterm /Early term /Term /Late term birth	%7/%50/%43/%0	%6/%25/%56/%12	%5/%50/%34/%11	%4/%26/%43/%9	%4/%26/%70/%0	12	17.56	0.129
Birth Weight(gr)	3153.17 ± 435.17	3251.25 ± 502.27	3191.38 ± 436.69	3052 ± 636.27	3193.70 ± 612.74	4	1.56	0.816
Birth length(cm)	49.91 ± 1.93	50.57 ± 1.60	49.75 ± 1.69	49.35 ± 2.76	50.71 ± 1.73	4	5.09	0.277
The time at NCU	1.05 ± 3.02	1.31 ± 3.02	0.57 ± 1.75	4.17 ± 18.73	2.95 ± 7.54	4	2.82	0.588
Staying at NCU (Yes/No)	%17/%83	%12/%88	%16/%84	%13/%87	%30/%70	4	2.88	0.577
Breastfeeding (Yes/No)	%90/%10	%93/%7	%100/%0	%90/%10	%100/%0	8	8.69	0.521
The time of breastfeeding (month)	6.45 ± 5.55	7.75 ± 5.56	9.47 ± 8.01	13.38 ± 8.01	8.54 ± 8.12	4	7.90	0.095
Neonatal bilirubinemia (Yes-Transient-mild /No)	%48/%52	%18/%82	%22/%78	%46/%54	%18/%82	8	9.86	0.275

LBW: Low Birth Weight NCU: Neonatal Intensive Care Unit.

diagnoses was statistically higher in the mirtazapine group than in the SSRI-mirtazapine combination group ($p = 0.006$). The number of previous relapses after treatment cessation was statistically higher in the SSRI-mirtazapine combination group than in the SSRI ($p = 0.002$) and the unmedicated patient group ($p = 0.002$). A psychiatric disorder diagnosed on admission was more severe in the SSRI-mirtazapine combination group than in the SSRI ($p = 0.003$), mirtazapine ($p = 0.001$) and the unmedicated patient groups ($p = 0.001$). Psychiatric disorder was less severe in the unmedicated patient group than in the SSRI ($p =$

0.00), mirtazapine ($p = 0.002$) and SSRI-mirtazapine combination groups ($p = 0.001$). The ratio of inpatient treatment was statistically higher in the SSRI-mirtazapine combination group than in the SSRI ($p = 0.002$) and unmedicated patient groups ($p = 0.001$).

Table 4 provides the mean gestational week of birth, rate of preterm birth, mean birth weight, mean birth length, requirement of NICU and mean duration of stay at the NICU in the groups. No differences were noted between SSRI-exposed, mirtazapine-exposed, SSRI-mirtazapine combination-exposed, unmedicated and healthy control groups with regard to the

Table 5. The investigation of the confounding effect of smoking and the severity of the disorder.

		¹ SSRI exposed (N = 40)	² Mirtazapine exposed (N = 16)	³ SSRI-mirtazapine exposed (N = 18)	⁴ Psychiatric diagnosis unmedicated (N = 23)	⁵ Healthy Control (N = 23)
Smoking						
Yes	Preterm Birth	1/12	0/7	1/7	1/4	2/2
No	(Yes/No)	2/25	1/8	0/9	0/18	1/16
Mantel-Haenszel	$p^{1vs 2}=0.646, p^{1vs 3}=0.792, p^{1vs 4}=0.875, p^{1vs 5}=0.554, p^{2vs 3}=0.509, p^{2vs 4}=0.541, p^{2vs 5}=0.614, p^{3vs 4}=0.683, p^{3vs 5}=0.335, p^{4vs 5}=0.448$					
Yes	Low Birth	0/13	0/7	1/7	1/4	1/3
No	Weight (Yes/No)	4/23	1/8	0/9	1/17	2/15
Mantel-Haenszel	$p^{1vs 2}=0.784, p^{1vs 3}=0.901, p^{1vs 4}=0.845, p^{1vs 5}=0.964, p^{2vs 3}=0.509, p^{2vs 4}=0.760, p^{2vs 5}=0.850, p^{3vs 4}=0.937, p^{3vs 5}=0.566, p^{4vs 5}=0.885$					
Yes	Staying at NICU	1/12	1/6	3/5	2/3	1/3
No	(Yes/No)	6/21	1/8	0/9	5/13	2/15
Mantel-Haenszel	$p^{1vs 2}=0.968, p^{1vs 3}=0.720, p^{1vs 4}=0.430, p^{1vs 5}=0.965, p^{2vs 3}=0.896, p^{2vs 4}=0.334, p^{2vs 5}=0.853, p^{3vs 4}=0.344, p^{3vs 5}=0.892, p^{4vs 5}=0.383$					
The severity of the disorder						
Mild to Moderate	Preterm Birth	1/14	1/8	0/1	3/17	
Severe	(Yes/No)	2/23	0/7	1/16	0/2	
Mantel-Haenszel	$p^{1vs 2}=0.723, p^{1vs 3}=0.796, p^{1vs 4}=0.948, p^{2vs 3}=0.571, p^{2vs 4}=0.767, p^{3vs 4}=0.320$					
Mild to Moderate	Low Birth	0/15	1/8	0/1	3/17	
Severe	Weight (Yes/No)	4/21	0/7	1/16	0/2	
Mantel-Haenszel	$p^{1vs 2}=0.786, p^{1vs 3}=0.615, p^{1vs 4}=0.613, p^{2vs 3}=0.571, p^{2vs 4}=0.767, p^{3vs 4}=0.320$					
Mild to Moderate	Staying at NICU	2/13	1/8	0/1	3/17	
Severe	(Yes/No)	5/20	1/6	3/14	0/2	
Mantel-Haenszel	$p^{1vs 2}=0.959, p^{1vs 3}=0.917, p^{1vs 4}=0.816, p^{2vs 3}=0.630, p^{2vs 4}=0.619, p^{3vs 4}=0.593$					

Table 6. Correlation of the sociodemographic and clinical properties of the women with psychiatric diagnosis.

	Pregnancy week as soon as relaps	Pregnancy week as soon as admission to hospital	The week of treatment onset	The duration of treatment at pregnancy (week)
Education			$r=-0.262^*$	$r=0.297^*$
Psychiatric disorder duration			$r=-0.250^*$	$r=0.350^*$
The time to relaps (month)	$r=0.415^{**}$	$r=0.343^*$	$r=0.403^{**}$	$r=-0.487^{**}$

* $p \leq 0.05$ ** $p \leq 0.001$ r = effect size

gestational week of birth, rate of preterm birth, birth weight, birth length, a requirement of NICU and duration of NICU stay.

Table 5 presents the analyses of the effects of confounding variables. All p values were larger than 0.05. The statistics revealed that smoking and the disorder's severity did not have any effect on the association between groups and birth outcomes.

Table 6 displays the clinically important correlations between the clinical properties and birth outcomes. Correlations that were significant but irrelevant to this study's aim were not reported. A negative correlation with small effect size was noted between the time of education and the week of treatment onset ($r = -0.262$); higher education levels were correlated with earlier treatment onset. Longer psychiatric disorder duration was correlated with an earlier week of treatment onset ($r = -0.250$) and longer duration of treatment at pregnancy with small effect size ($r = 0.350$). Increased time from the last relapse before pregnancy was positively correlated with a later pregnancy week relapse ($r = 0.415$), a later week of admission to hospital ($r = 0.343$), a later pregnancy week following the beginning of treatment (0.403) and shorter duration of treatment at pregnancy ($r = -0.487$).

Discussion

This study followed naturalistically and compared pregnant women with SSRI, mirtazapine, SSRI mirtazapine combination and unmedicated patient groups

for birth outcomes, alongside a healthy control group. No difference was observed with respect to birth week, birth weight and stay at NICU. Among all groups, the likelihood of a new diagnosis was highest in the mirtazapine group. The patients with more severe disorders and those with a higher number of relapses were treated with a combination of mirtazapine- SSRI. A long time from the last disease exacerbation in the prepregnancy was associated with the late onset of the psychiatric disorder during pregnancy. Longer psychiatric disorder duration was correlated with an earlier week of treatment onset.

No difference was observed between the medicated, unmedicated and healthy control groups with regard to the gestational week of birth and rate of preterm birth. In addition, SSRI, SSRI-mirtazapine combination and mirtazapine groups were similar in terms of birth week and the ratio of preterm birth. The studies have consistently revealed the association between antenatal psychiatric disorders and preterm birth [23–25]. However, studies are inconsistent regarding whether the treatment of psychiatric disorders prevents preterm birth. Venkatesh reported that after treatment of antenatal depression, no association was noted between preterm birth and depressive symptoms [25]. On the other hand, a meta-analysis reported the similarity between the medicated and unmedicated antenatal depression groups according to the time of birth [15]. It has been reported that SSRI exposed and mirtazapine exposed groups were similar in terms of the birth week [12,13].

No difference was observed with respect to the birth weight in the medicated, unmedicated and healthy control groups. Conflicting findings were recorded with respect to the relationship between psychiatric disorders and birth weight. A meta-analysis reported that birth weight was similar between the antenatal depressive and the healthy control group [16]. Another meta-analysis reported the significant association between antenatal depression and LBW [24]. LBW was 14% in the unmedicated patient group, compared to an 8% LBW in the healthy control group in our study. Additionally, the rate of LBW was higher in the unmedicated group than in the medicated groups. We suggested that the medication of psychiatric disorders could prevent LBW. However, the findings of this study should be cautiously reported due to our small sample size. The literature presents conflicting findings of the association between antidepressant usage and birth weight. A meta-analysis identified an association between antidepressant use and LBW [26]. However, another meta-analysis reported no association between birth weight and antidepressant use [27]. In this study, the comparison of birth weight revealed similarities between the SSRI, SSRI–mirtazapine combination and mirtazapine groups. This finding was consistent with the study of Winterfeld [12]. Although there were no differences between SSRI, mirtazapine and SSRI–mirtazapine combination groups with respect to birth weight, LBW was 7% in mirtazapine group, 6% in SSRI–mirtazapine combination group, and 10% in SSRI group. The treatment option that included mirtazapine seems to result in lower LBW rates than in the SSRI group. There might theoretically be a risk of higher birth weight in newborns due to weight gain and the increased risk of gestational diabetes in the mother. There is no available study that mentions mirtazapine use in pregnancy and higher birth weights of newborns. The study that included pregnant women who used SSRI, SNRI or mirtazapine during pregnancy found no risk for being LGA (large for gestational age) or macrosomia of newborns [28]. Although we did not control pregnant women's weight, and this was a limitation of our study, we informed patients about the effects of mirtazapine on weight gain before the beginning of treatment. Neither excessive weight gain nor gestational diabetes was found in women treated with mirtazapine. Further studies are needed to investigate whether mirtazapine is associated with an increased weight of newborns.

No difference was observed with regard to the requirement for neonatal intensive care and the duration of the NICU stay among the five groups in this study. The literature presents different results for the effect of antenatal psychiatric disorders of mothers on the duration of stay of the newborn in the NICU. A meta-analysis reported no effect of antenatal

depression on the requirement for neonatal intensive care [19]. On the other hand, several studies reported such an association [23]. The exposure to SSRIs in late pregnancy was associated with an increased rate of neonatal intensive care requirement [29,30]. In opposition to these studies the dosage of SSRI was found to be important; decreased dosages (≤ 20 mg paroxetine, ≤ 100 mg sertraline) were not associated with neonatal adaptation symptoms, but increased dosages were associated [30,31]. A possible explanation for the absence of differences between groups in terms of NICU stay in our study is the low dosages of antidepressants that were used. Consistent with our results, Smit observed similarity of infants who were exposed to mirtazapine and other antidepressants with regard to the rates of neonatal poor adaptation syndrome [32]. Premature birth and antidepressant discontinuation syndrome are some of the reasons for poor neonatal adaptation. Poor neonatal adaptation is associated with the requirement for neonatal intensive care. We contacted obstetricians and pediatricians before deliveries and provided information about the risk of neonatal discontinuation syndrome. Given the expected risk of neonatal discontinuation syndrome and an increased vigilance by the alerted pediatricians, no difference was observed among the medicated, unmedicated and healthy control groups with regard to the neonatal intensive care requirement. We recommended infant breastfeeding to all the patients. This suggestion might have resulted in the transient and self-limiting neonatal adjustment syndrome. A study that supports our results revealed that newborns who were exposed to antidepressants in the prenatal period and were breastfed were less likely to develop poor neonatal adaptation syndrome than those who were fed by formula [33]. A meta-analysis revealed a lower ratio of breastfeeding in women who had antenatal depression than in non-depressed women [16]. Patients may choose not to breastfeed on their own or as per the suggestion of other doctors (especially those who are not psychiatrists). We recommended maintaining the antidepressant treatment after delivery to decrease the risk of relapse in pregnant women who had been receiving medical treatment in the third trimester. In association with the recommended continuation of breastfeeding, no differences were observed among the groups with regard to the ratio and time of breastfeeding in this study.

No difference was observed with regard to the birth outcomes in the medicated and unmedicated patient groups in this study. The psychiatric disorders were less severe in the unmedicated group in comparison with the SSRI ($p = 0.001$), mirtazapine ($p = 0.008$) and with the SSRI–mirtazapine combination group ($p = 0.001$). Regular interviews, which aimed at strengthening the social support system, were

conducted with the unmedicated pregnant women. If necessary, the unmedicated pregnant women underwent non-pharmacological treatments, including cognitive behavioral, interpersonal or supportive psychotherapeutic approaches in our unit. These approaches might reduce the negative consequences of unmedicated psychiatric disorders. Regardless of drug use, access to the health care system by pregnant women with psychiatric disorders might have had a positive effect on pregnancy. Considering psychiatric health care may also be related to the ability and facility to receive other health services. The use of health services during pregnancy might play a role in preventing the negative consequences of maternal psychiatric disorders. Thus, in our study, unmedicated patient pregnant women could not be accepted as an untreated group. Specific studies compared the effects of untreated and treated antenatal psychiatric disorders on birth outcomes. One study reported that birth weight and birth week were lower in the newborns of untreated antenatal depressive women than those of antenatal depressive women treated with SSRI during pregnancy [34]. On the other hand, and consistent with our results, the aforementioned study revealed that the birth weight and birth week were similar between the non-depressed healthy control and treated depressed groups [34].

The rate of new diagnosis was statistically higher in the mirtazapine group compared with the SSRI-mirtazapine combination group. Mirtazapine is a possible treatment option for newly diagnosed patients in this observational study. Mirtazapine is a useful option especially when the illness presents with insomnia and loss of appetite. The symptoms of anxiety or depression accompanied by insomnia or loss of appetite were treated by mirtazapine as monotherapy.

The psychiatric illnesses in the SSRI-mirtazapine combination group followed a more severe and chronic course. It is possible that the population studied is a high-risk sample. The history of the previous relapse after treatment cessation was statistically higher in the SSRI-mirtazapine combination group than in the SSRI and unmedicated groups. The psychiatric disorder observed immediately after admission was more severe in the SSRI-mirtazapine combination group than in the SSRI ($p = 0.006$), mirtazapine ($p = 0.006$) and unmedicated patient groups ($p = 0.001$). The ratio of inpatient treatment was statistically higher in the SSRI-mirtazapine combination group than in the SSRI group ($p = 0.003$) and unmedicated groups ($p = 0.002$). On the other hand, the ratio of the previous relapse between the SSRI-mirtazapine combination and mirtazapine groups showed no difference; as the mirtazapine group substantially comprised newly diagnosed patients, which presented no previous relapse history, these newly diagnosed patients were thus excluded in the analysis. The ratio of inpatient

treatment was similar between the SSRI-mirtazapine combination and mirtazapine groups. As a result, the SSRI group was differentiated from the SSRI-mirtazapine group with regard to less severe psychiatric disorders and lower inpatient treatment rates. Although the severity of illness in the SSRI-mirtazapine combination group was higher than in the mirtazapine group, the ratio of inpatient treatment between the SSRI-mirtazapine combination and mirtazapine groups were similar. This result was interpreted as follows: mirtazapine was a useful monotherapy option for patients with less severe disorders at low doses and patients with severe disorders and had to be hospitalized at high doses.

The use of paroxetine by patients' own will in the first trimester was related to the difficulty of quitting paroxetine due to severe withdrawal symptoms. Paroxetine use was continued by two patients on their own after the detection of unplanned pregnancies. These patients declared that they had attempted to quit paroxetine but could not resist owing to the withdrawal symptoms and gradually began using it again. A congenital anomaly known as bilateral pes equinovarus was detected in one infant who had been exposed to paroxetine in the first trimester. The study reported that the risk of pes equinovarus was elevated with paroxetine use (OR 9.2) [35]. Except for this risk, no congenital anomalies were observed in the whole group. The literature reports that except paroxetine, exposure to SSRI [36] and mirtazapine [32,37] during pregnancy is not associated with an increased risk of major anomalies. The study reported that there were no differences between the SSRI group and a mirtazapine group with respect to birth defects [12].

The time from the last disorder exacerbation in the prepregnancy period to relapse in the pregnancy period was defined as the time to relapse. A longer time to relapse was associated with late-onset of psychiatric disorders during pregnancy. The length of the remission period before pregnancy indicates a late period of relapse in pregnancy. In addition, longer psychiatric disorder duration was correlated with earlier treatment requirement and longer treatment duration during pregnancy. According to these results, even before pregnancy, clinicians can predict the course of the disorder, evaluate the relapse risk and also make a plan in terms of quitting the treatment or not.

The higher education level was correlated with the early onset of treatment in our sample. Cooper reported that high education level is a predictor of antidepressant exposure in pregnancy [38]. We speculated that a higher education level may be associated with lower prejudice about treatment and the ability for earlier hospital admission.

This study has several limitations. The major limitation is the size of the sample groups. Further studies with larger sample sizes are needed to provide an

accurate assessment. The other limitation is the information related to the sociodemographic data and the usage and amount of cigarette consumption obtained from the self-reporting. Thus, these data carry the risk of recall bias. The comparisons made according to the SSRI group were not for specific SSRI agents. 23 patients initiated the treatment in the first trimester, 38 in the second, and 13 in the third trimester. Except for two patients, the others who started to use the antidepressant medication in the first or second trimester continued the treatment to the end of pregnancy, and therefore we could not compare the trimester-specific effects of antidepressants. As our unmedicated patient group received either therapy or psychological support, this group cannot be designated an untreated group. Thus, if a medically unfollowed patient group was included, we could learn the actual effects of untreated maternal psychiatric disorder on birth outcomes. Undoubtedly, non-treatment of pregnant patients who had been admitted to our hospital is an unethical approach. Other women with antenatal psychiatric disorders were admitted during the postpartum period. We could have included this group as an untreated patient group, but the information, including the properties of psychiatric disorders and birth outcomes, would be self-reported and have the risk of recall bias. Finally, our sample comprised pregnant women with different diagnoses. This study design may be repeated with a homogenous group in the future.

On the other hand, this study controlled the groups for several potential confounding effects (e.g. smoking and the severity of the disorder). The information was entered and documented in the database at the same time at the visit. Therefore, the prospective documentation system enabled us to reach the data correctly and prevented recall bias for these parameters. These aspects contributed to the increased impact of the study. Additionally, this study presents a three-year experience of the clinicians in terms of mirtazapine usage at pregnant women.

Use of mirtazapine in pregnancy has not been adequately addressed in the literature. It is expected that this study may contribute to the literature in light of perinatal psychiatry unit data. This study revealed the lack of difference between the SSRI and mirtazapine usage during pregnancy with regard to the birth outcomes of newborns. Similar birth outcomes could present clinicians with the option of prescribing mirtazapine as a safe alternative to SSRI in the treatment of antenatal psychiatric patients. The neonatal outcomes of the severe maternal psychiatric disorder group, who were medicated with SSRI or mirtazapine, were similar to those of the unmedicated moderate-severity maternal psychiatric disorder group. The risk of high-severity psychiatric disorder that was medicated with SSRI or mirtazapine or the combination of these agents might have been balanced with the risk

of unmedicated low to moderate-severity psychiatric disorder. Finally, this study supports the idea that the management of maternal psychiatric disorders may present positive effects regardless of the severity of the psychiatric disorder.

Ethics statement

The study comply with the principles of the Declaration of Helsinki.

The study was approved by the local ethics committee of University of Health Sciences Istanbul Mazhar Osman Bakirkoy Mental Health and Neurological Diseases Training and Research Hospital.

Disclosure statement

No potential conflict of interest was reported by the authors.

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