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In vitro effects of sertraline and escitalopram on rat uterine smooth muscle

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MAIN POINTS

- This study examined the efficacy of sertraline and escitalopram on the contractility of rat uterine muscles.
- SSRIs dose-dependently reduce myometrial contraction AUC in vitro.
- Sertraline decreases AUC under oxytocin in nonpregnant and pregnant rats.
- Escitalopram shows no significant pairwise effects after Holm-Bonferroni correction.

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ABSTRACT

Aim: Depressive disorders affect around 10% of pregnant women. Antidepressant use during pregnancy is important for maternal and fetal health. Although studies link antidepressants to risks of spontaneous abortion, preterm labor, and postpartum hemorrhage, their direct effects on the myometrium remain unclear. This study investigated the effects of sertraline and escitalopram on spontaneous and oxytocin-induced contractions in rat myometrial tissue.

Materials and Methods: 6 pregnant and 14 nonpregnant female Sprague-Dawley rats were used in the study. Myometrial strips measuring 1x0.2x0.2 centimeters were obtained from rats. Female rats were decapitated on day 18-20 of gestation. In oxytocin-induced and spontaneous contractions, sertraline and escitalopram were added cumulatively at concentrations of 1 μM, 3 μM and 10 μM in pregnant and nonpregnant rat groups and AUC (Area Under the Curve), frequency and amplitude values were recorded.

Results: Regression analysis demonstrated a significant dose-dependent decrease in AUC (particularly under oxytocin). Holm-Bonferroni adjusted Wilcoxon tests confirmed that sertraline reduced AUC during oxytocin-induced contractions in both nonpregnant and pregnant strips, while escitalopram showed no significant effects on AUC, amplitude, or frequency.

Conclusion: In vitro, AUC decreased dose-dependently---particularly with sertraline during oxytocin-induced contractions---while the effects of escitalopram were inconsistent. These results may support cautious use of the lowest effective dose in pregnancy and motivate further translational work.

Keywords: Myometrium, Pregnancy complications, Selective serotonin reuptake inhibitors, Uterine contractions

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INTRODUCTION

Pregnancy is a physiological process accompanied by hormonal, biological, and psychosocial changes. These adaptations may predispose individuals to psychiatric conditions, with depressive disorder being the most prevalent. Affecting approximately 280 million people globally, depressive disorder exhibits a higher incidence in women, particularly during pregnancy and the postpartum period [1]. In low- and middle-income countries, the prevalence of antenatal depression is estimated at 10% [2], while one in ten pregnant women in the United States receives antidepressant therapy during gestation [3,4].

The diagnosis and management of depressive disorder during pregnancy require a specialized approach, because reluctance in the initiation of the treatment may adversely affect maternal and fetal outcomes. While psychotherapy remains the first-line intervention for mild to moderate depression, severe cases necessitate pharmacological treatment [5,6]. Selective serotonin reuptake inhibitors (SSRIs), such as sertraline, citalopram, and escitalopram, are frequently prescribed due to their favorable safety profile in pregnancy [7].

Although antidepressant use during pregnancy has been associated with obstetric complications—including preterm birth, spontaneous abortion, neonatal adaptation syndrome, persistent pulmonary hypertension, cardiac malformations, and postpartum hemorrhage— untreated depression carries comparable risks [8–10]. A systematic review further highlighted that adverse outcomes linked to untreated depression

often mirror those observed in treated populations [11]. Additionally, untreated depressive disorder may exacerbate behaviors detrimental to maternal and fetal health, such as poor self-care, inconsistent prenatal monitoring, nutritional deficiencies, smoking, substance use, and elevated suicide risk [12].

SSRIs are known to exert nonspecific effects beyond their primary mechanism of action, including relaxation of smooth muscle in structures such as blood vessels [13,14], the vas deferens [15], and the ileum [16]. While epidemiological studies suggest a potential association between SSRI use and myometrial dysfunction—manifesting as preterm labor, postpartum hemorrhage, or spontaneous abortion—the precise mechanisms underlying these complications, particularly their impact on uterine contractility, remain poorly understood. Consequently, further investigation into the effects of widely used antidepressants on uterine muscle activity is warranted. This study aims to evaluate the *in vitro* effects of sertraline and escitalopram on spontaneous and oxytocin-induced contractions in rat myometrium, utilizing isolated uterine smooth muscle tissue from both pregnant and nonpregnant rats.

MATERIALS AND METHODS

Experimental procedures

The protocol of this study was reviewed and approved by the Karadeniz Technical University Animal Research Ethics Committee (No: 2021–7; February 8, 2021). All animal experiments were carried out in compliance with the Republic of Türkiye's national legislation and internationally accepted guidelines for the care and use of laboratory animals. In study, 6 pregnant and 14 nonpregnant adult Sprague-Dawley female rats, weighing between 250-300 grams and six months old, obtained from the Surgical Application Research Center of Karadeniz Technical University, were used. The animals were kept in an environment with 65-70% humidity at 22-25°C under a 12-hour light-dark cycle. They were fed with standard pelleted rat food and tap water (ad libitum).

Female rats that were determined to be in the appropriate cycle (in proestrus and estrus phases) were mated with an adult male Sprague-Dawley rat in single cages. Vaginal smear method was applied to determine pregnancy in rats that were allowed to mate.

Rats that were determined to be pregnant were decapitated without anesthesia on days 18-20 of pregnancy, starting from day 0 (because anesthetic drugs may have effects on smooth muscle function). After decapitation, the uteruses of the rats were quickly removed and 4 myometrial strips of 1x0.2x0.2 centimeters were obtained from each pregnant rat and 2 myometrial strips of 1x0.2x0.2 centimeters were obtained from nonpregnant rats. Since spontaneous contractions were not observed in 3 myometrial strips obtained from pregnant rats and 1 myometrial strip obtained from nonpregnant rats, they were excluded from the study.

The obtained myometrial strips were hung vertically in an isolated organ bath containing Krebs solution with a constant temperature of 37°C and a pH of 7.4, continuously gassed with normoxic gas (95% O2 + 5% CO2). One end of the myometrial strips was connected to an isometric force transducer (BIOPAC, FDT 05, MAY, Turkey), while the other end was fixed to the bottom of the organ bath. The myometrial strips were washed with fresh solutions every 15 minutes for 60 minutes and monitored under 1 g resting tension. After regular spontaneous contractions were observed, contractions were recorded for 10 minutes.

Experimental groups were determined using a sealed opaque envelope system to ensure random allocation and minimize selection bias. Sertraline (Catalog no:14839, Cayman, USA) and escitalopram (Catalog no:22405, Cayman, USA) to be used in the study were prepared by dissolving them in distilled water. Sertraline was dissolved in a beaker containing 37°C warm water using a vortex mixer prior to the experiment. In pregnant and nonpregnant rat groups, sertraline and escitalopram were added cumulatively at concentrations of 1 μM, 3 μM and 10 μM, respectively, and 10-minute recordings were taken for each dose. For oxytocin-induced contractions, 0.1 nM oxytocin (Synpitan Forte, Deva, Istanbul) was added to the organ bath and 10-minute recordings were taken. Then, with the cumulative addition of sertraline and escitalopram, 10-minute recordings were taken. Isometric tension and its changes were recorded using a physiological data acquisition and recording system (Biopac MP100, MAY, Turkey) via an isometric force transducer and computer. Measurement of AUC, frequency and amplitude values were made using Acq-Knowledge 4.0 (USA) software (Figure 1).

Sample size

Power analysis (G*Power 3.1) with α=0.05 (two-tailed) and power=0.80 indicated n=6 independent samples per group, sufficient to detect ~20% changes in AUC in paired within-strip comparisons. To adhere to 3R principles, multiple strips were obtained from each uterus so that tissues from 6 pregnant and 14 nonpregnant rats yielded n=6 for each of the eight conditions. This approach aligns with prior *in vitro* myometrial studies using 5–8 strips per condition [17,18].

Statistical analysis

Frequency was analyzed as absolute counts. AUC and amplitude were normalized within strip by setting the baseline (control or oxytocin) to 100% and expressing subsequent responses as % of baseline. Because sample sizes were small (5–7 strips/group) and normality was mixed (Shapiro–Wilk), we used nonparametric tests uniformly. Planned within-strip comparisons of each dose (1, 3, 10 μM sertraline or escitalopram) versus baseline were performed with the Wilcoxon signed-rank test, with Holm–Bonferroni adjustment across the three contrasts. To assess the overall dose–response trend while accounting for repeated measurements within strip, we

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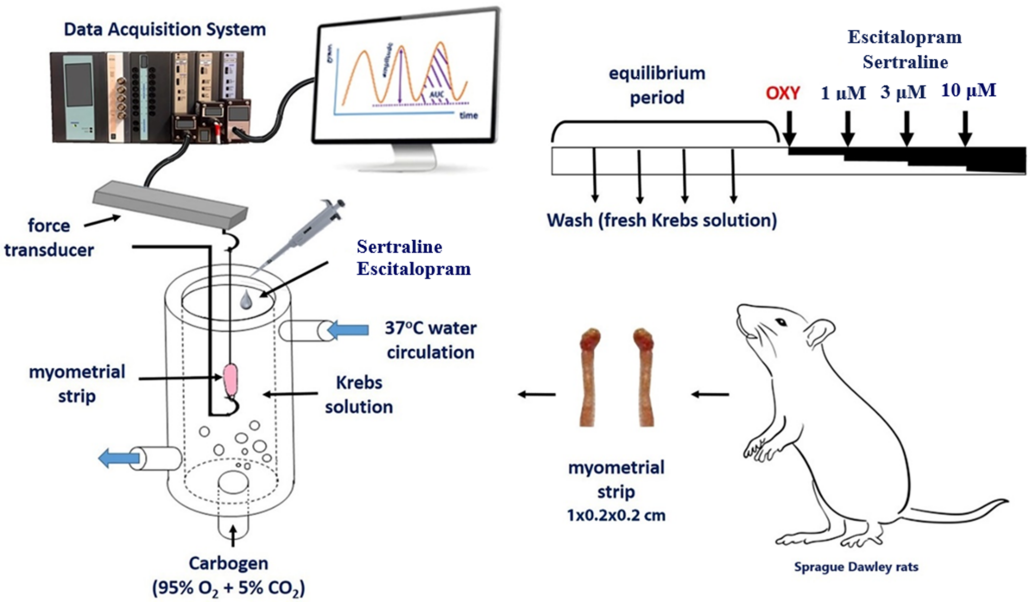

Figure 1. Schematic diagram of the experimental design and protocol. Myometrial strips were mounted in a double-jacketed, temperature-controlled organ bath containing physiological saline solution, continuously gassed with normoxic. Smooth muscle contractile force was recorded using an isometric force transducer and analyzed with computer software. Following a 60-minute equilibration period under resting tension, spontaneous (unstimulated) or oxytocin-induced contractions were elicited. Cumulative concentrations of sertraline and escitalopram were then applied at 10-minute intervals, and contractile responses were evaluated in terms of amplitude, area under the contractility curve, and contraction frequency. OXY = oxytocin.

fitted linear mixed-effects models with a random intercept for strip in IBM SPSS Statistics v25 (MIXED, REML; covariance type: variance components). Dose (µM) was entered as a continuous covariate (baseline coded as 0 µM); for normalized outcomes, the slope (β) is reported as % per µM. Monotonic direction was summarized with Spearman's ρ. Data are presented as median (IQR); two-sided $p<0.05$ was considered statistically significant.

RESULTS

After the tissue samples were subjected to an adaptation process for 60 minutes under 1 g resting tension, spontaneous contractions occurred in 48 of the 52 tissue samples, and 4 tissue strips that did not show regular spontaneous contractions after the adaptation process were excluded from the study.

The effect of sertraline on myometrial contractions

The cumulative effects of sertraline on spontaneous and oxytocin-induced contractions were evaluated in myometrial strips from pregnant and nonpregnant rats and summarized in Table 1.

In myometrial strips from nonpregnant adult female rats (n=6), cumulative effects of sertraline (1, 3, and 10 µM) to the spontaneous contractions were nonspecific as shown by the AUC, amplitude, or frequency after Holm–Bonferroni adjustment (paired Wilcoxon signed-rank test, exact, two-sided) (Table 2).

In myometrial strips from nonpregnant adult female rats (n=7) under oxytocin-induced contractions, cumulative effects of sertraline (1, 3, and 10 µM) were again nonspecific in terms of amplitude after Holm–Bonferroni adjustment (paired Wilcoxon signed-rank test, exact, two-sided), whereas AUC decreased significantly at all doses under oxytocin whereas, the frequency decreased at 10 µM under oxytocin (Table 2).

In myometrial strips from pregnant adult female rats (n=5), cumulative sertraline effects on (1, 3, and 10 µM) spontaneous contractions where nonspecific in terms of AUC, amplitude, or frequency after Holm–Bonferroni adjustment (paired Wilcoxon signed-rank test, exact, two-sided) (Table 2).

In myometrial strips from pregnant adult female rats (n=7) under oxytocin-induced contractions, cumulative sertraline effects (1, 3, and 10 µM) were nonspecific in frequency after Holm–Bonferroni adjustment (paired Wilcoxon signed-rank test, exact, two-sided). AUC decreased significantly only at 10 µM after adjustment, while amplitude showed nominal decreases at 3 and 10 µM that that showed no significant difference after multiplicity correction (Table 2).

The effect of escitalopram on myometrial contractions

The cumulative effects of escitalopram on spontaneous and oxytocin-induced contractions were evaluated in myometrial strips from pregnant and nonpregnant rats and are summarized in Table 3.

In myometrial strips from nonpregnant adult female rats (n=6), cumulative escitalopram (1, 3, and 10 µM) effects on spontaneous contractions were insignificant in terms of AUC, amplitude, or frequency after Holm–Bonferroni ad-

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Table 1. The effect of sertraline on myometrial contractions.

		Sertraline					
		Nonpregnant			Pregnant		
Contraction Type	Drug Concentration μM	Median (IQR) Frequency	Median (IQR) amplitude %	Median (IQR) AUC %	Median (IQR) Frequency	Median (IQR) amplitude %	Median (IQR) AUC %
Spontaneous	Control	7.5(8-5)	100	100	7(13.5-6.5)	100	100
	1 (μM)	8(9-5)	100.5(102-95.25)	96.5(98-77)	8(13.5-6.5)	127(149-76)	87(125.5-64.5)
	3 (μM)	7.5(8-4)	100(102.75-90.25)	87.5(91-71)	6(12.5-6)	91(180-76,5)	79(132-61.5)
	10 (μM)	7(9-4)	94.5(102-82)	87(91-70)	7(12.5-5.5)	88(162-60)	73(105-57.5)
Oxytocin-Induced	Control	10(11-9)	100	100	11(11-8)	100	100
	0.1 (nM) oxytocin	12(14.5-11.5)	106(116.5-97)	152(213-128)	11(12-9.5)	231(263-130.5)	216(302.5-164.5)
	1 (μM)	13(13.5-11)	109(120.5-97)	138(188.5-120)	11(11-10)	186(205-141)	195(248.5-123.5)
	3 (μM)	11(11-9.5)	106(122-100)	118(152.5-107.5)	10(11-8.5)	198(219.5-110)	142(250-125)
	10 (μM)	8(9-6.5)	94(102.5-93)	108(116-92)	9(9.5-7.5)	148(173-90)	105(196-98.5)

AUC: Area Under the Curve.

Table 2. Dose-dependent comparisons versus baseline.

		Wilcoxon for Sertraline											
		Nonpregnant						Pregnant					
Contraction Type	Drug Concentration μM	AUC		Frequency		Amplitude		AUC		Frequency		Amplitude	
		P (two-sided)	P (adjusted)	P (two-sided)	P (adjusted)	P (two-sided)	P (adjusted)	P (two-sided)	P (adjusted)	P (two-sided)	P (adjusted)	P (two-sided)	P (adjusted)
Spontaneous	1 (μM)	0.03	0.09	1.00	1.00	0.87	1.00	0.62	1.00	1.00	1.00	0.62	1.00
	3 (μM)	0.03	0.09	0.50	1.00	1.00	1.00	0.62	1.00	0.62	1.00	0.81	1.00
	10 (μM)	0.03	0.09	0.81	1.00	0.22	1.00	0.37	1.00	0.75	1.00	1.00	1.00
Oxytocin-Induced	1 (μM)	0.02	**0.048§**	0.62	0.62	0.84	1.00	0.03	0.06	0.75	0.75	0.16	0.16
	3 (μM)	0.02	**0.048§**	0.06	0.13	1.00	1.00	0.047	0.06	0.28	0.56	0.03	0.09
	10 (μM)	0.02	**0.048§**	0.02	**0.048§**	0.03	0.09	0.016	**0.048§**	0.14	0.42	0.03	0.09

AUC: Area Under the Curve, bold and § indicate statistically significant differences compared to control ($p<0.05$. Wilcoxon signed-rank test, Holm–Bonferroni–adjusted).

Table 3. The effect of escitalopram on myometrial contractions.

		Escitalopram					
		Nonpregnant			Pregnant		
Contraction Type	Drug Concentration μM	Median (IQR) Frequency	Median (IQR) amplitude %	Median (IQR) AUC %	Median (IQR) Frequency	Median (IQR) amplitude %	Median (IQR) AUC %
Spontaneous	Control	8.5(9-5)	100	100	8(9-8)	100	100
	1 (μM)	7(9-4)	101.5(103-99)	92.5(94-89)	9(10-8)	119(159-105)	123(145-95)
	3 (μM)	7(8-4)	99(102-98)	88.5(95-88)	9(10-8)	93(103-80)	86(93-78)
	10 (μM)	6.5(8-5)	99(102-88)	84.5(89-79)	9(10-8)	91(98-43)	81(98-51)
Oxytocin-Induced	Control	4.5(5-3)	100	100	8(12-8)	100	100
	0.1 (nM) oxytocin	11(12-9)	133(239-106)	285(315-167)	8.5(12-7)	209.5(318-143.5)	291.5(377.5-227.25)
	1 (μM)	11(12-9)	134(207-112)	265(294-153)	10.5(11-7)	187(425-128,5)	298.5(359.75-205)
	3 (μM)	10(10-9)	137.5(208-113)	251.5(269-133)	10(11-7)	190.5(320.25-121.5)	257.5(325-184)
	10 (μM)	10(10-9)	138(209-115)	236.5(251-125)	9.5(12-7)	172(314.5-112.5)	231.5(297-165.5)

AUC: Area Under the Curve.

justment (paired Wilcoxon signed-rank test, exact, two-sided) (Table 4).

In myometrial strips from nonpregnant adult female rats (n=6) under oxytocin-induced contractions, cumulative ef-

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Table 4. Dose-dependent comparisons versus baseline.

		Wilcoxon for Escitalopram											
		Nonpregnant						Pregnant					
Contraction Type	Drug Concentration μM	AUC		Frequency		Amplitude		AUC		Frequency		Amplitude	
		P (two-sided)	P (adjusted)	P (two-sided)	P (adjusted)	P (two-sided)	P (adjusted)	P (two-sided)	P (adjusted)	P (two-sided)	P (adjusted)	P (two-sided)	P (adjusted)
Spontaneous	1 (μM)	0.06	0.09	0.31	0.94	0.53	1.00	0.31	0.63	1.00	1.00	0.12	0.37
	3 (μM)	0.03	0.09	0.41	0.94	0.81	1.00	0.12	0.37	0.50	1.00	0.31	0.63
	10 (μM)	0.03	0.09	0.69	0.94	0.50	1.00	0.62	0.63	0.75	1.00	0.62	0.63
Oxytocin-Induced	1 (μM)	0.09	0.09	0.50	0.50	0.84	1.00	0.44	0.44	0.87	1.00	0.62	1.00
	3 (μM)	0.03	0.09	0.06	0.19	0.72	1.00	0.06	0.19	1.00	1.00	0.56	1.00
	10 (μM)	0.03	0.09	0.12	0.25	0.78	1.00	0.06	0.19	0.81	1.00	0.56	1.00

AUC: Area Under the Curve, bold and § indicate statistically significant differences compared to control (p<0.05. Wilcoxon signed-rank test, Holm–Bonferroni–adjusted).

Table 5. Linear Mixed-Effects Model (LMM) analysis of dose-dependent contractility trend.

			Slope β (%/dose code*)	95% CI	p	Spearman ρ
Sertraline	Nonpregnant spon	AUC	−1.43	[−2.28, −0.59]	<0.001	−0.76
		Amplitude	−0.03	[−0.12, 0.05]	0.46	−0.06
		Frequency	−0.88	[−1.65, −0.10]	0.03	−0.18
	Nonpregnant Oxytocin Induced	AUC	−5.96	[−7.95, −3.97]	<0.001	−0.57
		Amplitude	-4.44	[-9.27, 0.39]	0.07	-0.22
		Frequency	−0.48	[-0.64, -0.32]	<0.001	−0.66
	Pregnant spontaneous	AUC	−1.85	[−4.92, 1.22]	0.24	−0.35
		Amplitude	−0.09	[−0.23, 0.06]	0.24	−0.09
		Frequency	−0.12	[−4.59, 4.35]	0.96	−0.14
	Pregnant Oxytocin Induced	AUC	−9.33	[−13.21, −5.44]	<0.001	−0.39
		Amplitude	−0.19	[−0.34, −0.04]	0.01	−0.41
		Frequency	−9.38	[−16.87, −1.88]	0.01	−0.34
Escitalopram	Nonpregnant spontaneous	AUC	−1.52	[−2.17, −0.86]	<0.001	−0.75
		Amplitude	−0.02	[−0.12, 0.07]	0.65	−0.15
		Frequency	−1.00	[−1.93, −0.06]	0.04	−0.14
	Nonpregnant Oxytocin Induced	AUC	−3.66	[−5.38, −1.95]	<0.001	−0.64
		Amplitude	−0.36	[−0.59, −0.14]	0.002	−0.48
		Frequency	−0.29	[−1.25, 0.68]	0.56	0.07
	Pregnant spontaneous	AUC	−2.16	[−3.54, −0.78]	0.005	−0.62
		Amplitude	−0.05	[−0.15, 0.05]	0.34	−0.09
		Frequency	−1.44	[−2.79, −0.09]	0.04	−0.36
	Pregnant Oxytocin Induced	AUC	−6.97	[−10.61, −3.32]	<0.001	−0.45
		Amplitude	0.06	[−0.12, 0.23]	0.53	0.08
		Frequency	−3.40	[−14.28, 7.49]	0.54	−0.16

*Cl: Confidence Interval, AUC: Area Under the Curve, dose code: control, 1 μM, 3 μM, 10 μM.

fects of escitalopram (1, 3, and 10 μM) insignificant in terns of AUC, amplitude, or frequency after Holm–Bonferroni adjustment (paired Wilcoxon signed-rank test; exact, two-sided) (Table 4).

In myometrial strips from pregnant adult female rats (n=5), cumulative effects of escitalopram (1, 3, and 10 μM) during spontaneous contractions were insignificant in terms of in AUC, amplitude, or frequency after Holm–Bonferroni adjustment (paired Wilcoxon signed-rank test, exact, two-sided) (Table 4).

In myometrial strips from pregnant adult female rats (n = 6) under oxytocin-induced contractions, cumulative effects of

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escitalopram (1, 3, and 10 μM) were insignificant in terms of AUC, amplitude, or frequency after Holm–Bonferroni correction (paired Wilcoxon signed-rank test, exact, two-sided) (Table 4).

Analysis of the dose-response trend

Across datasets, dose–response modeling with a linear mixed-effects model (LMM) framework showed that increasing dose was associated with a reduction in myometrial contraction, most consistently for AUC and often for amplitude, while effects on frequency were smaller or dataset-dependent. Importantly, even in conditions where individual dose vs control comparisons (Wilcoxon) did not reach significance, the mixed-effects slope (β) indicated a negative trend across the given doses, and Spearman's ρ supported the monotonic decrease. Collectively, these findings indicate that higher cumulative doses tend to inhibit the myometrial contraction (Table 5).

DISCUSSION

In our *in vitro* rat model, both SSRIs demonstrated a dose-dependent reduction in total contractile activity (AUC) across spontaneous and oxytocin-induced conditions. This was reflected by a negative dose–response slope ($\beta < 0$) in the linear mixed-effects model (LMM), with the notable exception of sertraline's effect on spontaneous contractions in pregnant strips. The inhibitory trend was most pronounced under oxytocin stimulation. For sertraline, the LMM indicated significant AUC reductions under oxytocin in both (e.g., nonpregnant: $\beta = -5.96$ %/μM, 95% CI −7.95 to −3.97; pregnant: $\beta = -9.33$ %/μM, 95% CI −13.21 to −5.44). Conversely, amplitude and frequency varied by condition and group, failing to form a consistent pattern.

Holm–Bonferroni-adjusted Wilcoxon comparisons confirmed a consistent reduction in AUC only for sertraline under oxytocin stimulation; in contrast, escitalopram showed no statistically significant changes in AUC, amplitude, or frequency after correction for multiple comparisons. Corroborating our findings, previous studies have reported that sertraline exerts a relaxant effect on smooth muscle, particularly at higher concentrations and under induced contractile conditions [13, 19]. Although escitalopram has likewise been shown to induce dose-dependent relaxation in various smooth muscle tissues (20), no significant changes were observed in our study via pairwise comparisons. This discrepancy may stem from the inherent limitations of the Wilcoxon test; particularly with small sample sizes and stringent multi-comparison corrections, it may fail to detect subtle but consistent effects. In contrast, statistical methods that directly model ordinal dose–response relationships, such as the LMM and Spearman's rho coefficient, offer greater statistical power to detect uniform changes distributed across dose levels.

Myometrial contraction depends not only on IP_3-mediated Ca^{2+} release from the sarcoplasmic reticulum (SR) but also on extracellular Ca^{2+} influx through L-type Ca^{2+} channels [21]. Previous reports indicating that sertraline and escitalopram can inhibit Ca^{2+} currents at micromolar concentrations align with the patterns observed here [19, 20]. Under conditions of elevated Ca^{2+} demand (such as oxytocin stimulation), a channel-level "brake" on stimulus-dependent Ca^{2+} entry may reduce total activity (AUC) and lower contraction frequency at higher concentrations without necessarily suppressing amplitude in a uniform manner. Furthermore, escitalopram is known to inhibit not only calcium channels but also voltage-dependent potassium (Kv) channels in vascular smooth muscle [22]. The possibility that these ion channel effects are less pronounced in uterine smooth muscle, or require higher concentrations to manifest, is consistent with the smaller negative dose–response slope observed for escitalopram ($\beta < 0$) and the absence of significant effects in pairwise Wilcoxon comparisons. These findings likely reflect drug-specific pharmacodynamic properties and inherent limitations in statistical power.

If SSRIs attenuate oxytocin-dependent contractility, exposure during pregnancy may contribute to variability in intrapartum uterotonic responsiveness, potentially slowing labor progression or increasing the need for augmentation. Nevertheless, these *in vitro* findings are hypothesis-generating and do not, in isolation, warrant changes in clinical practice. Observational studies have reported a consistent association between SSRI use and postpartum hemorrhage [10, 23, 24], whereas associations with preterm birth [25] and miscarriage [26] remain more heterogeneous. In the clinical context, the dose-dependent inhibition of myometrial contractions observed in our study aligns with the principles of utilizing the lowest effective dose, avoiding polypharmacy, and selecting agents with favorable reproductive safety profiles to maintain a patient-centered risk–benefit balance that safeguards maternal mental health [27, 28].

Limitations

Our study has several limitations. First one is the fact that current study is an ex vivo study. Species differences and the absence of investigations regarding the endocrine, vascular, and inflammatory components of the effects may limit extrapolation of our results to human subjects .

Another limitation is the small number of subjects and the Holm-Bonferroni adjustment reduces sensitivity of pairwise tests; thus, subtle dose-specific effects may be under-detected even when a global trend exists. Furthermore, we did not perform blocking experiments (e.g., nifedipine, SOCE inhibitors) or direct Ca^{2+} imaging/patch-clamp, so ion-channel involvement is inferred from the pattern and prior literature rather than demonstration with our results.

In the present study, we did not assess the probable indirect SSRI effects via uteroplacental or fetoplacental perfusion

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(e.g., 5-HT–sensitive vasoreactivity); such changes could contribute to clinical outcomes (postpartum hemorrhage, spontaneous abortion, preterm labor) even in the absence of strong direct myometrial effects at therapeutic exposures. We did not test the serotonin–oxytocin crosstalk. Although serotonin can be uterotonic and oxytocin may increase local serotonin availability (e.g., by limiting uptake in mast cells), our setup did not test these interactions explicitly. We did not assess how depression itself (neuroendocrine/inflammatory alterations) might modify uterine contractility; disease-model studies are warranted.

CONCLUSION

Our data demonstrate a negative dose–response slope ($\beta < 0$) for AUC with SSRI treatment—most robustly for sertraline under oxytocin stimulation—while amplitude and frequency exhibit condition-dependent variability. These findings suggest drug-specific, rather than uniform class-wide, effects on myometrial contractility. Such results underscore the need for future research to delineate dosing strategies that minimize obstetric risks while preserving antidepressant efficacy.

Ethics Committee Approval: The protocol of this study was reviewed and approved by the Karadeniz Technical University Animal Research Ethics Committee (No: 2021–7; February 8, 2021).

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Conflict of Interest: The authors declare that they have no conflict(s) of interests.

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