BMC Pediatrics

RESEARCH

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The association between gestational selective serotonin reuptake inhibitor (SSRI) treatment and newborn thyroid screen: a large-scale cohort study

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Abstract

Background The diagnosis of depression or anxiety treated by SSRIs has become relatively common in women of childbearing age. However, the impact of gestational SSRI treatment on newborn thyroid function is lacking. We explored the impact of gestational SSRI treatment on newborn thyroid function as measured by the National Newborn Screening (NBS) Program and identified contributory factors.

Methods An observational large-scale study of mother-infant dyads of liveborn infants delivered between 2011 and 2022. The Israeli NBS Program thyroid dataset [total thyroxine (TT4) obtained between 36-72 h after delivery] was linked with the electronic medical records of mothers and their infants born at Lis Maternity and Women's Hospital, to generate a unified database. The MDClone big data platform was utilized to extract maternal, perinatal, and neonatal characteristics from the medical records of mother-infant dyads. Only term liveborn infants born to mothers without documented thyroid disease and/or chronic medication administration, except for SSRIs, were included in order to minimize potential confounding effects on the infant's thyroid function. Group stratification relied on the documentation of gestational SSRIs treatment. The variables of interest were maternal, pregnancy, delivery, and perinatal characteristics of the mother–infant dyads. Multivariable forward linear regression model was applied to evaluate explanatory variables for newborn total thyroxine (TT4) levels.

Results Out of 105,928 infant-mother dyads, 2321(2.2%) mothers had been treated with SSRIs during pregnancy. The SSRI-treated mothers were older (34.8 ± 4.7 vs 32.6 ± 4.8 years, $p < 0.001$) and had a higher pre-pregnancy body mass index (23.4 ± 4.5 vs 22.7 ± 4.1, $p < 0.001$), but similar mean weight gain (13 kg) during pregnancy. Cesarean delivery was more common among SSRI-treated mothers than in the general population ($p < 0.001$). Infants of SSRI-treated mothers had lower WHO-classified birthweight z-scores (-0.25 ± 0.93 vs -0.04 ± 0.92, $p < 0.001$) and a higher rate of small-for-gestational-age infants (13.4% vs 8.2%, $p < 0.001$). A multivariable forward linear regression model revealed that SSRI treatment during pregnancy was not a significant contributor to TT4 levels ($p = 0.497$).

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Conclusions SSRI treatment during pregnancy had no direct effect upon the newborn's adaptation of the hypothalamic-pituitary-thyroidal axis, but several other maternal and delivery characteristics were revealed to possibly impact newborn thyroid function.

Keywords Antidepressant drug, In vitro fertilization (IVF), Oxytocin, Pregnancy, Thyroid function

Introduction

Fetal growth and development can be adversely affected by exposure to environmental factors during pregnancy, including those that occur as early as conception [1, 2]. Furthermore, the intrauterine milieu, reflecting the maternal health condition, dictates risk for various diseases during postnatal life [3–6]. Modulation of thyroid function has been suggested as one of the metabolic programming mediators that links between prenatal and postnatal life [7–9].

Depression and anxiety are serious morbidities among women of childbearing age [10–12]. Selective serotonin reuptake inhibitors (SSRIs), the first-line medication prescribed for these indications, act by inhibiting the presynaptic plasma membrane serotonin transporter mediating the reuptake of serotonin into the presynaptic terminal [13]. SSRI use in pregnancy has increased over the years, with a reported prevalence ranging from 1.3 to 12% and varying by geography [14–16]. Although the safety profile of SSRI use during pregnancy is encouraging [17], some studies have shown a link between maternal gestational SSRI treatment and adverse birth outcomes, including premature birth [18], intrauterine growth restriction and low birthweight [15, 19], and persistent pulmonary hypertension [20]. It was also questioned whether gestational SSRI exposure may disrupt fetal hormonal functions, specifically, the secretion of growth hormone [21] and thyroid hormone [22].

The postnatal adaptation of the hypothalamic-pituitary-thyroidal (HPT) axis is sensitive to a range of factors, including maternal, delivery, and neonatal characteristics [23, 24]. The aim of this study was to explore the impact of gestational SSRI treatment on newborns' thyroid function as measured by the National Newborn Screen (NBS) Program and to identify contributory factors.

Methods

Study design and population

We conducted a retrospective observational study of infant-mother dyads of liveborn infants delivered at Lis Maternity and Women's Hospital, Tel Aviv Sourasky Medical Center (TASMC), between January 1, 2011, and January 1, 2022. Datasets from TASMC and the Israeli NBS Program were linked to generate a mother-infant database unified with infant thyroid function results.

The NBS Program Database provides information on early detection of congenital hypothyroidism by routinely screening all newborns through measurement of total thyroxine (TT4) at 36–72 h of age [25]. Thyrotropin (thyroid-stimulating hormone [TSH]) measurements were also obtained in cases with TT4 results which fell in the daily lowest 10th centile (range of daily 10th centile: 8–12 μg/dL). The Israeli NBS program's thyroid dataset was queried to create a list of all the neonates born at TASMC during the study period. The medical records of mothers and their infants born at Lis Maternity Hospital at TASMC were accessed with the MDClone platform from MDClone© Ltd in Beer Sheva, Israel [26]. After obtaining IRB approval, the platform analyzed large medical datasets using sophisticated algorithms, and generated deidentified versions of the data for use in the study. SSRIs that were used for MDClone search were those approved by the Israeli Ministry of Health and prescribed by the Israeli healthcare providers [27].

Included were infants born at term for whom data on both mother and infant were available in the hospital's database. To minimize potential confounding effects on thyroid function of the mother or infant, only infants born to mothers without documented thyroid disease and/or chronic medication administration, except for SSRIs, were included. Excluded from the study were infants who were preterm (gestational age [GA] < 37 weeks) due to perinatal morbidity which could affect the HPT axis postnatal adaptation, as well infants for whom GA-adjusted thyroid function levels were lacking [28]. The dyads were categorized into two groups: the gestational SSRI treatment group (exposed cohort) and the general population (non-exposed cohort) (Fig. 1).

Outcome measurement

The variables of interest included data on maternal, pregnancy, delivery process, and perinatal characteristics of the mother–infant dyads. The information in the electronic medical files contains both self-reported patient information, measured parameters, laboratory results, and physician's notes on diagnoses, management, and surveillance.

The mother's information retrieved from the maternity hospital database included: reported SSRI treatment during the current pregnancy, obstetric history (gravidity,

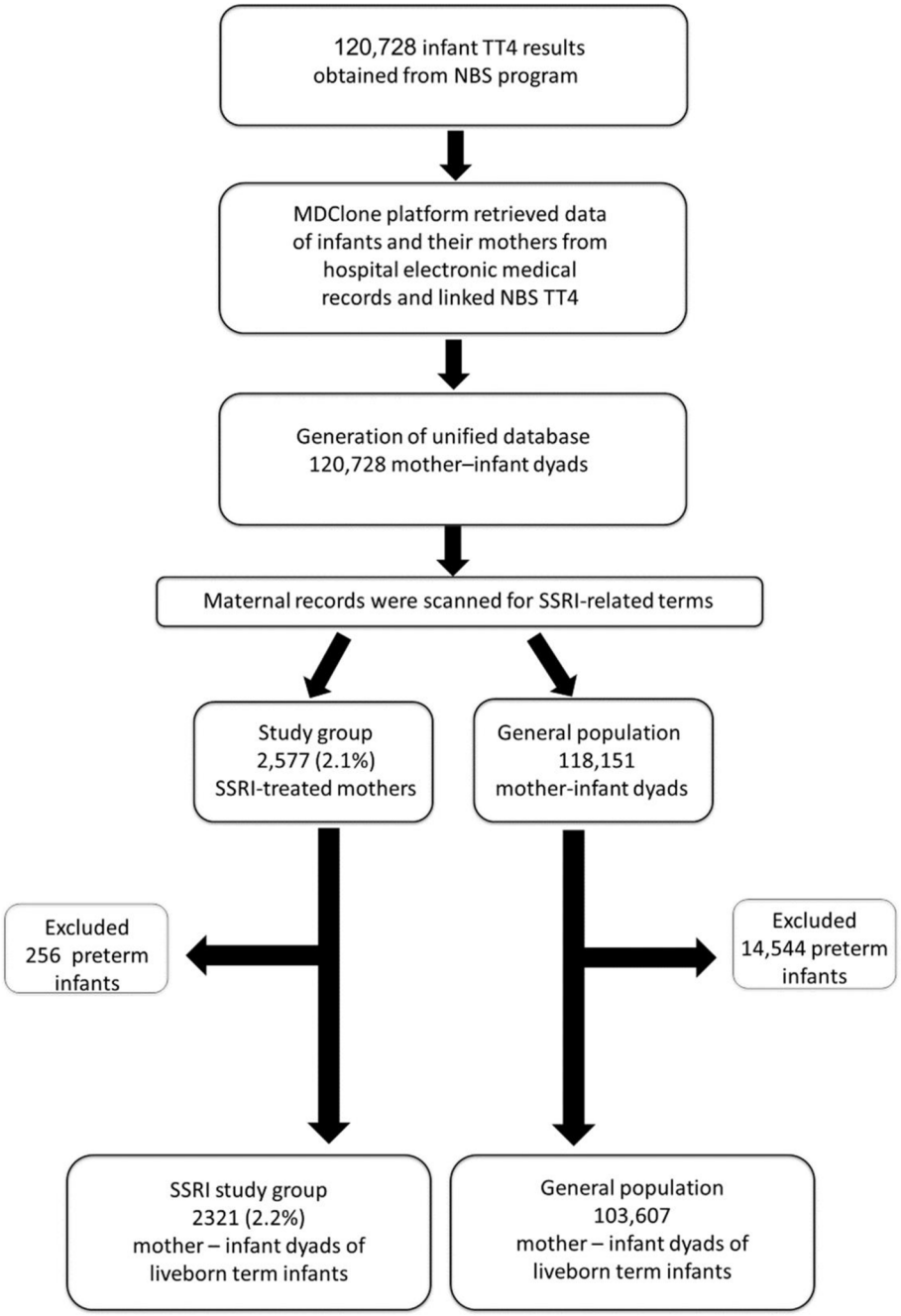

Fig. 1 Flow chart of study design and patient selection

parity, history of abortion and ectopic pregnancy, and previous live births), age at current delivery, and anthropometric measurements (height, reported weight before pregnancy, and measured weight before delivery). The collected data on the course of pregnancy included: number of fetuses (singleton/twins), method of conception (spontaneous, in-vitro fertilization [IVF], and non-IVF assisted reproduction), infections during pregnancy (Group B Streptococcus [GBS] and active cytomegalovirus [CMV]) as well as gestational morbidity (gestational diabetes, hypertension, and proteinuria). Information collected on delivery included maternal vital signs (pulse [beats per minute], systolic and diastolic blood pressure [mmHg], medication administered during labor [oxytocin, antibiotics], use of anesthesia (none, local, regional [spinal/epidural], or general), mode of delivery

(spontaneous vaginal, vaginal assisted, elective cesarean section, or emergent cesarean section), amniotic membranes and fluid (premature rupture of membranes [PROM], stained amniotic fluid), and placenta characteristics (intact, incomplete, or abnormal).

The data retrieved from the medical files of infants included newborn characteristics (sex, gestational age [weeks], birthweight [kg], presentation [vertex, face/brow, breech, other]), APGAR score at 1 and 5 min after birth, temperature [°C], and department of hospitalization (nursery/ neonatal intensive care unit [NICU]). Data obtained from the NBS program included newborn thyroid functions (total T4 [μg/dL]), and TSH [mU/L]).

Study variable definitions

The pregestational body mass index (BMI) was calculated as the pre-pregnancy weight (kg) divided by squared height (meters). The weight gain during pregnancy was calculated as the measured weight before delivery minus the reported weight before pregnancy [29].

Methods of conception were divided into spontaneous pregnancy, IVF, and non-IVF assisted reproduction. Non-IVF assisted reproduction was defined as the use of any methods of reproduction assistance, including, but not limited to, intrauterine insemination, ovulation induction medications, or a combination of the two [30].

The recommended infections screen during pregnancy includes GBS screening by vaginal and rectal swab performed between 36 and 38 weeks of gestation [31]. Screening for specific CMV IgM antibodies in CMV seronegative mothers was aimed at detecting gestational CMV infection [32]. Gestational diabetes (GDM) was defined according to Carpenter and Coustan criteria using the 3-h 100-g oral glucose tolerance test [33].

Multiple readings of pulse and systolic and diastolic blood pressure were recorded for each mother in order to obtain a representative measurement of maternal vital signs during delivery, and the average of these measurements was calculated. Antibiotics were administered during labor for all accepted indications, including prophylaxis before cesarean section. Vaginal-assisted delivery referred to the use of any instruments to assist a vaginal delivery, including vacuum assistance. PROM was defined as the rupture of the amniotic sac prior to the onset of labor. Meconial or bloody amniotic fluid was defined as being "stained". Presentation that was neither vertex, face/brow, nor breech was defined as “other”, and it included compound, transverse, or diagonal presentation. The placenta was categorized by gross appearance as being intact, incomplete (in which persistence of part of the placenta warranted a gynecological procedure) or abnormal (in which size, color, shape, and/or general appearance were abnormal).

Newborn data-corrected birthweight z-scores were calculated for infants by means of PediTools Electronic Growth Chart Calculators, based upon the WHO growth chart for term infants [34]. Birthweight that was appropriate for gestational age (AGA) was defined as corrected birthweight z-scores of −1.28 to 1.28, small for gestational age (SGA) as birthweight z-scores < −1.28, and large for gestational age (LGA) as birthweight z-scores > 1.28 [35].

Length of hospitalization for mothers and their infants was calculated as the time that had elapsed between admission and release from the hospital.

Statistical analyses

Data were analyzed by the IBM SPSS software (IBM SPSS Statistics for Windows, Version 28; IBM Corp., Armonk, NY). Continuous data were presented as mean ± standard deviation (normal distribution) or median [interquartile range] (skewed distribution), and as number and percentage for categorical variables. Differences in continuous data between groups were examined using independent-sample t-tests (normally distributed data) or Mann–Whitney U-tests (skewed data). The chi-squared tests were used to examine the differences in categorical data. A multivariable linear regression model was used to evaluate the contribution of various factors (maternal, delivery-related, and infant characteristics) which affected TT4 levels. In the first block SSRI treatment was entered while in the second block which was conducted in a forward selection, the following variables entered the model: maternal age, IVF pregnancy, oxytocin administration, cesarean delivery, infant’s sex (male), gestational age and birthweight z-score. A P-value of ≤ 0.05 was considered significant.

Results

During the study period, newborn thyroid screen results were available for 120,728 infants liveborn at Lis Maternity and Women’s Hospital of TASMC to mothers with no chronic medication treatment other than SSRIs. Excluded were 14,800 infant-mother dyads of preterm infants (gestational age < 37 weeks). In total, 105,928 infant-mother dyads of term infants were included, of whom 2,321 (2.2%) were flagged with gestational SSRI use (Fig. 1).

Maternal and gestational characteristics of the mother-infant dyads of the gestational SSRI group compared to the general population are presented in Table 1. Mothers who were treated by SSRIs were older (mean age 34.8 ± 4.7 years vs. 32.6 ± 4.8 years, $p < 0.001$) and more likely to be nulliparous (60.6% vs 42.1%,

Table 1 Characteristics of mother and pregnancy of mother-infant dyads with gestational SSRI use compared to the general population

	General population	SSRI exposed group	*P* value
Number	103,607	2,321	
Obstetric history			
Gravidity	2 [1, 3]	2 [1, 3]	< 0.001
Nulliparity, n (%)	43,519 (42.1)	1405 (60.6)	< 0.001
Parity	1 [0, 2]	0 [0, 1]	< 0.001
Abortion	0 [0, 1]	0 [0, 1]	< 0.001
Ectopic pregnancy	1483 (1.4)	50 (2.2)	< 0.001
Previous live births	1 [0, 2]	0 [0, 1]	< 0.001
Anthropometrics			
Height, meters	1.64 ± 0.06	1.64 ± 0.06	0.596
Pregestational weight, kg	61.2 ± 11.7	63.1 ± 12.5	< 0.001
Pregestational BMI, kg/m^2	22.7 ± 4.1	23.4 ± 4.5	< 0.001
Pregnancy			
Age at delivery, years	32.6 ± 4.8	34.8 ± 4.7	< 0.001
Twin gestation, n (%)	2157 (2.1)	25 (1.1)	< 0.001
Method of conception, n (%)			
Spontaneous pregnancy	94,252 (91.0)	1918 (82.6)	< 0.001
IVF	6079 (5.9)	923 (12.6)	
Non-IVF assisted reproduction	3276 (3.2)	110 (3.7)	
Gestational morbidity, n (%)			
Gestational diabetes	4826 (4.7)	140 (6.0)	0.001
Hypertension	888/77,972 (1.1)	31/1820 (1.7)	< 0.001
Proteinuria	632/73,354 (0.9)	39/1709 (2.3)	< 0.001

The data are expressed as number and (percent), median [interquartile range], and mean ± standard deviation. Statistical significance is set at $P \leq 0.05$. For the cohort as a whole, screen for gestational hypertension was available in 75.3% and screen for proteinuria in 70.5%

n number, *kg* kilograms, *BMI* body mass index, *IVF* in vitro fertilization

$p < 0.001$) compared to mothers in the general population. Mothers treated by SSRIs had a higher pregestational BMI (23.4 ± 4.5 kg/m^2 vs 22.7 ± 4.1 kg/m^2, $p < 0.001$) compared to mothers in the general population, albeit similar mean weight gain of 13 kg.

Methods of conception differed significantly between the two groups, with more mothers treated by SSRIs having undergone assisted fertility treatments than the general population: specifically, they had higher rates of IVF (12.6% vs 5.9%, $p < 0.001$) and non-IVF assisted reproduction use (3.7% vs 3.2%, $p < 0.001$). Pregnancies of mothers treated by SSRIs were characterized by increased rates of gestational complications, such as gestational diabetes (6.0% vs 4.7%, $p = 0.001$), hypertension (1.7% vs 1.1%, $P < 0.001$), and proteinuria (2.3% vs 0.9%, $p < 0.001$), compared to the general population.

In total, 32,492 (30.6%) mothers completed the GBS screen, and 7075 (21.9%) of those cultures were positive for GBS. There were no significant group differences in either the rate of screening or the rate of infection. CMV seroconversion was present in 2.5% of the mothers treated by SSRIs compared to 2.3% of mothers in the general population; there were no significant group differences in either the rate of CMV screening or the rate of seroconversion.

Labor and delivery-related characteristics of mother-infant dyads with gestational SSRI use compared to those of the general population are presented in Table 2. The mode of delivery differed between the groups, with a significantly increased rate of cesarean Sects. (28.7% vs 19.7%, $p < 0.001$) and increased need for instrument assistance in vaginal delivery (17.7% vs 8.5%, $p < 0.001$) in mothers treated by SSRIs. Those mothers also had an increased rate of stained amniotic fluid (30.1% vs 17.1%, $p < 0.001$). Medication administration during labor differed significantly between groups, with increased use of oxytocin (53.8% vs 40.9% $p < 0.001$), antibiotics (45.1% vs 35.4%, $p < 0.001$), and anesthesia (86.0% vs 75.6%, $p < 0.001$) in the SSRI group compared to the general population.

Infant characteristics stratified according to gestational SSRI exposure are presented in Table 3. Despite

Table 2 Characteristics of labor and delivery of mother-infant dyads with gestational SSRI use compared to the general population

	General population	SSRI exposed group	*P* value
Number	103,607	2,321	
Maternal vital signs			
Pulse beats/min	84.0 ± 17.3	81.9 ± 14.8	< 0.001
Systolic blood pressure, mmHg	119.7 ± 10.1	118.3 ± 17.3	< 0.001
Diastolic blood pressure, mmHg	71.7 ± 9.6	71.0 ± 13.2	< 0.001
Amniotic membranes and fluid, n (%)			
PROM	4210 (4.1)	104 (4.5)	0.016
Stained amniotic fluid	17,686 (17.1)	699 (30.1)	< 0.001
Fetal presentation, n (%)			
Vertex	99,101 (95.7)	2221 (95.7)	0.272
Face/brow	123 (0.1)	6 (0.3)	
Breech	4069 (3.9)	88 (3.8)	
Other	314 (0.3)	6 (0.3)	
Mode of delivery, n (%)			
Spontaneous vaginal	76,128 (73.5)	1360 (58.6)	< 0.001
Vaginal assisted	7,104 (6.9)	292 (12.6)	
Elective cesarean section	11,492 (11.1)	356 (15.3)	
Emergent cesarean section	8883 (8.6)	312 (13.4)	
Medication administered during labor, n (%)			
Oxytocin	42,388 (40.9)	1072 (53.8)	< 0.001
Antibiotics	36,726 (35.4)	1274 (45.1)	< 0.001
Anesthesia, n (%)			
No anesthesia	25,328 (24.4)	325 (14.0)	< 0.001
Local	1042 (1.0)	12 (0.5)	
Regional (spinal/epidural)	76,111 (73.5)	1950 (84.0)	
General	1126 (1.1)	34 (1.5)	
Placenta, n (%)			
Intact	101,525 (98.0)	2258 (97.3)	< 0.001
Incomplete	963 (0.9)	27 (1.2)	
Abnormal	1119 (1.1)	36 (1.6)	
Hospitalization			
Duration, days	2.9 ± 1.7	3.2 ± 2.1	< 0.001

The data are expressed as number and (percent), mean ± standard deviation. Statistical significance set at $P \leq 0.05$

min minutes, *mmHg* millimeters of mercury, *n* number, *PROM* premature rupture of membranes

clinical similarity in gestational age between the groups (39.6 ± 1.1 weeks for the entire cohort), infants in the SSRI group were significantly smaller, had lower birthweight z-scores (−0.25 ± 0.93 vs −0.04 ± 0.92, $p < 0.001$), and more frequently categorized as SGA (13.4% vs 8.2%, $p < 0.001$) compared to the general population. NICU hospitalization was almost three times more common among the infants in the SSRI group (6.5% vs 2.2%) and their mean hospitalization duration was longer ($p < 0.001$). The mean TT4 levels did not differ between the groups, however, a greater proportion of newborns in the SSRI group required TSH testing due to a relatively low TT4 level (14% vs 9.1%, $p < 0.001$). Notably, the TSH levels did not differ between the SSRI group and the general population.

A multivariable forward linear regression model was applied to evaluate contributing factors for newborn TT4 levels. Included in the final model were only the variables that were significantly associated with TT4 values, apart from gestational SSRI treatment, which was not associated with TT4 levels. The final model for higher newborn TT4 ($R^2 = 0.022$, $p < 0.001$) included younger maternal age ($p < 0.001$), IVF-conceived pregnancy ($p < 0.001$), oxytocin administration during delivery ($p < 0.001$), cesarean delivery ($p = 0.003$), female sex ($p < 0.001$), older GA ($p < 0.001$), and higher birthweight

Table 3 Characteristics of newborns in mother-infant dyads with gestational SSRI use compared to the general population

	General population	SSRI exposed group	*P* value
Number	103,607	2,321	
Male sex, n (%)	53,298 (51.4)	1,220 (52.6)	0.147
Gestational age, weeks	39.6 ± 1.1	39.2 ± 1.1	< 0.001
Birthweight, kg	3.291 ± 0.423	3.191 ± 0.427	< 0.001
WHO birthweight, z-scores	−0.04 ± 0.92	−0.25 ± 0.93	< 0.001
Birthweight categories, n (%)			
Small for gestational age	8453 (8.2)	312 (13.4)	< 0.001
Appropriate for gestational age	88,327 (85.3)	1906 (82.1)	
Large for gestational age	6827 (6.6)	103 (4.4)	
APGAR score			
1 min	9 [9]	9 [8, 9]	< 0.001
5 min	10 [10]	10 [9, 10]	< 0.001
Temperature, ºC	36.9 ± 0.3	36.9 ± 0.2	0.304
Hospitalization			
Nursery, n (%)	101,329 (97.8)	2171 (93.5)	< 0.001
NICU, n (%)	2278 (2.2)	150 (6.5)	
Duration, days, n (%)	2.4 ± 2.4	2.7 ± 2.9	< 0.001
Newborn thyroid screen			
Total T4, µg/dL	14.97 ± 3.70	14.96 ± 3.80	0.847
TSH, n (%)	9454 (9.1%)	325 (14%)	< 0.001
TSH, mU/L	4.7 [2.9, 7.7]	4.7 [2.7, 7.3]	0.432

The data are expressed as number and (percent), median [interquartile range], mean ± standard deviation. Statistical significance set at $P \leq 0.05$

n number, *kg* kilograms, *WHO* World Health Organization, *APGAR* appearance (skin color), pulse, grimace (reflex), activity (muscle tone) and respiration, *NICU* neonatal intensive care unit, *Total T4* total thyroxine, *TSH* thyroid-stimulating hormone

z-scores ($p < 0.001$) (Fig. 2). Maternal pregestational BMI and weight gain during pregnancy were not associated with newborn TT4 levels and therefore were not included in the model.

Discussion

We analyzed the characteristics of the mother-infant dyads of mothers treated with SSRIs during pregnancy to establish whether such treatment might affect the postnatal function of the newborn's HPT axis. The results of our analyses revealed that it did not have any direct effect on the infant's thyroid function. Our analyses did, however, reveal that the SSRI-treated mothers were older, that more of them were nulliparous, and that they more commonly conceived via IVF compared to the general population. They also had increased gestational morbidity as well as greater need for medical intervention during labor (drugs and instrumental delivery), and gave birth to smaller infants. Each of those characteristics may have affected the newborn thyroid screen levels, while gestational SSRI use alone did not.

Various aspects of maternal health, including nutrition, stress levels, and exposure to medication may affect the development and metabolic programming of the offspring [35, 36]. Infants exposed to an intrauterine environment influenced by maternal depression and anxiety may show compromised extrauterine adaptation [37]. Epigenetic modifications to fetal DNA have been suggested as a link between maternal stress and anxiety and the child's health [37]. While SSRI treatment can alleviate psychological distress, it does not eliminate all the circumstances affecting the intrauterine environment. Indeed, we identified several characteristics in the mother-infant dyads of mothers treated with SSRIs, which may play a role in the postnatal adaptation of the HPT axis.

Conception of the index pregnancy in mothers treated with SSRIs was associated with an increased utilization of assistive reproduction technology (ART). While there is insufficient evidence to suggest that SSRI treatment itself induces or reduces infertility [38], depression and anxiety may compromise fertility [39], which may further be augmented by infertility [40]. Increased gestational and obstetric complications have been described in IVF pregnancies, however, most were attributed to the maternal preconception characteristics [41]. IVF in our cohort was identified as an effector of newborn TT4 levels. Other studies have suggested that IVF may induce fetal

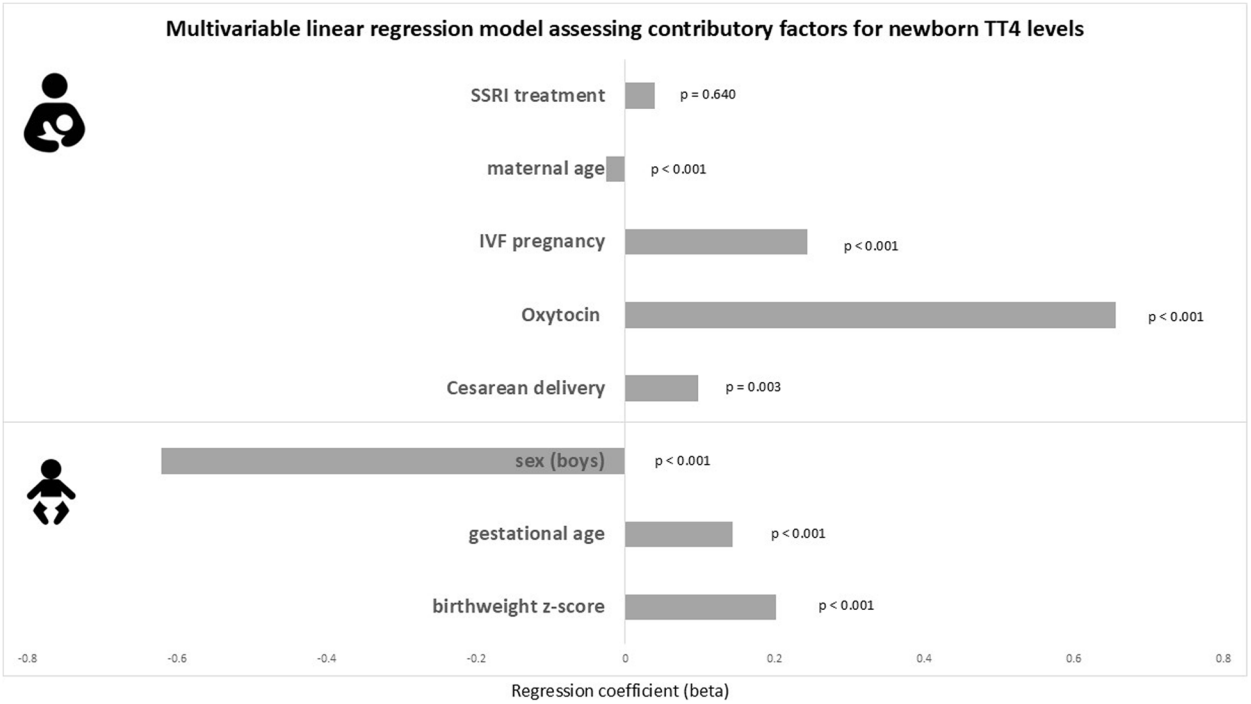

Fig. 2 Graphic presentation of the multivariable forward linear regression model applied to evaluate contributing factors for newborn TT4 levels. Included in the final model were only the variables that were significantly associated with TT4 values, apart from gestational SSRI treatment, which was not associated with TT4 levels (R2 = 0.022, $p < 0.001$)

epigenetic alterations, which could have long-term health consequences [42]. The combined effect of the maternal characteristics, the conception process, and the complicated gestational course observed in mothers treated with SSRIs may provide an explanation for the compromised fetal growth observed in their infants. Both hormonal and epigenetic alterations may serve as moderators of future health consequences for these infants.

Our study found that mothers treated with SSRIs were more likely to be older and nulliparous, which are known risk factors for pregnancy complications. Advanced maternal age, especially at first delivery, has been linked with increased risk for pregnancy complications [43, 44], and older nulliparous women have a lower probability of achieving a vaginal delivery [45]. In our study, only 56.8% of mothers treated with SSRIs achieved a vaginal delivery, and of those, there was a double risk for instrumental assistance.

Cesarean delivery has both short- and long-term implications on the health of the mother and her infant [46]. The mode of delivery is crucial in determining the newborn's acquisition of intestinal microbiota [47]. Cesarean birth prevents the beneficial exposure to maternal vaginal microbiota [48], which may predispose the offspring to metabolic disorders during childhood and adulthood [49]. Our study results demonstrated that infants born via cesarean section had unique postnatal HPT axis adaptation, unlike previous studies that reported no interaction between mode of delivery and newborn thyroid function [50]. Variations in the mode of delivery also result in differences in the use of anesthesia, with increased use of epidural anesthesia in mothers treated with SSRIs. This is particularly concerning since a recent study suggested that there is an increased risk for autism spectrum disorder in the offspring who have been exposed to intrapartum epidural analgesia [51].

Mothers treated with SSRIs had a higher utilization of oxytocin during labor, indicating a potential interaction between SSRIs and the intrinsic oxytocin hormone. Studies measuring oxytocin levels in patients with depression under SSRIs treatment presented inconclusive results [52]. Preliminary data in animal models suggest that chronic SSRI treatment induced delayed ejaculation in males due to variable degree of desensitization of 5-HT(1A) receptors on oxytocin neurons [53]. It is possible that SSRIs interfere with the mother's intrinsic oxytocin secretion during the progression of labor, necessitating medical intervention to promote uterine contractions. Our findings revealed that oxytocin administration during labor was associated with elevated levels of newborn TT4. This may be explained by the cross-talk between oxytocin and thyroid

hormone. Oxytocin has been shown to interfere with the synthesis and release of thyroid-releasing hormone (TRH) and suppress TRH-induced TSH release [54]. Conversely, thyroid hormone was found to bind to the promotor of oxytocin and increase its expression [54]. Our previous research also indicated an increased rate of oxytocin administration during labor in newborns with permanent congenital hypothyroidism [55]. However, the mechanism by which oxytocin administration during labor affects the HPT axis function in newborns has yet to be fully elucidated.

Infants born to mothers treated with SSRIs were smaller and had an increased rate of SGA, which could be attributed to the direct pharmacological effect of SSRIs. Term infants born to mothers treated with SSRIs had higher rates of NICU hospitalization and longer duration of stay, indicating increased perinatal morbidity. These adverse outcomes warrant attention since they may increase the risk of infection and complications for the newborn [56, 57]. The increased neonatal morbidity may also trigger parental psychological distress and potentially damage the early development of the mother-infant relationship [58]. Compromised fetal growth, a complex perinatal course, and maternal postpartum depression have been linked to increased risk of metabolic complications in offspring [59, 60], highlighting the need for further studies to evaluate the growth and development patterns of children who were exposed to SSRIs in utero.

Although our study provides important insights into the effects of gestational SSRI treatment on the HPT axis of infants, it is not without limitations. Firstly, our data obtained from the computerized database includes self-reported information, such as general health of the mother, obstetric history, gestational SSRI treatment, and pregestational weight. Secondly, our study lacks specific information on the type of SSRIs used, as well as their dose, duration of treatment, and compliance. It also lacks objective information on socioeconomic circumstances and lifestyle habits which may affect maternal health. Thirdly, the observational design of the study precludes our ability to establish causality between SSRI treatment and the distinct characteristics observed in the mother-infant dyads. Analyses of large-scale datasets may reveal statistical significance, but clinical significance could be uncertain, and the results should be interpreted with caution. Despite these limitations, our study has several strengths. The uniformity of obstetric protocol of a single medical center and the comprehensive data obtained from the Obstetric and Neonatal Departments of the Maternity Hospital are its major strengths. Furthermore, we utilized a large dataset comprising numerous variables to investigate a broad spectrum of factors that could potentially correlate with the outcomes of the thyroid screening for newborns. Finally, the comprehensive medical care provided to all pregnant citizens and non-citizen residents in Israel probably limits socioeconomic bias in healthcare.

Conclusions

The findings of our large-scale population-based cohort study have demonstrated that mother-infant dyads with gestational SSRI treatment have unique characteristics. While the function of the neonatal thyroid axis may have been affected by those factors, it was not directly affected by SSRI treatment. The role of neonatal thyroid secretion in modulating infants' metabolic outcomes remains to be elucidated. Additional research is necessary to investigate the various effects of gestational SSRI treatment on short-term and long-term outcomes for mothers and infants, including both term and preterm newborns.

Acknowledgements

The authors thank Esther Eshkol for editorial assistance and Eyal Egoz for accessing the MDClone platform. A portion of this research was presented at ENDO 2023, Chicago, USA.

Authors' contributions

O.R. made a substantial contribution to the curation of data, interpretation of data, and drafting of the article. E.C.S. made a substantial contribution to the curation of data, interpretation of data, and revision of the article for important intellectual content. M.Y.G. performed the statistical analysis, interpreted the data, and revised the article for important intellectual content. S.A. made a substantial contribution to the curation of data and revised the article for important intellectual content. R.M., J.H. and L.H. made a substantial contribution to the curation and interpretation of data analysis and revised the article for important intellectual content. Y.L. made a substantial contribution to the design of the study, interpretation of data analysis, and revised the article for important intellectual content. A.B. made a substantial contribution to the conception and design of the study, interpretation of data analysis and drafting of the article, and critically revised the article, incorporating contributions from the coauthors. A.B. is the guarantor of this work, and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and approved the final version.

Funding

No funding was received for this article.

Data availability

Anonymized data that underlie the results reported in this article can be made available upon reasonable request to the corresponding authors and will require the completion of a data processing agreement.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board (IRB) of the the Tel Aviv Medical Center (IRB No. 0030–22-TLV) according to the Declaration of Helsinki. Informed consent by the participants was waived since the data were retrieved from the subjects' medical records and all personal identification was anonymized. The data were handled in accordance with the principles of Good Clinical Practice and in compliance with ethical standards. This study was also performed in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

Competing interests
The authors declare no competing interests.

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Received: 1 March 2024 Accepted: 20 January 2025
Published online: 29 January 2025

References

1. de Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. Aust N Z J Obstet Gynaecol. 2006;46(1):4–14. https://doi.org/10.1111/j.1479-828X.2006.00506.x.
2. Barker DJ. Maternal nutrition, fetal nutrition, and disease in later life. Nutrition. 1997;13(9):807–13. https://doi.org/10.1016/s0899-9007(97)00193-7.
3. Huang X, Xiang H, Bao J, et al. The effects of intrauterine growth on physical and intellectual development of one-year-old infants: a study on monochorionic twins with selective intrauterine growth restriction. J Obstet Gynaecol. 2023;43(1):2125300. https://doi.org/10.1080/01443615.2022.2125300.
4. Falkner B. Maternal and gestational influences on childhood blood pressure. Pediatr Nephrol. 2020;35(8):1409–18. https://doi.org/10.1007/s00467-019-4201-x.
5. Brener A, Lebenthal Y, Levy S, Dunietz GL, Sever O, Tauman R. Mild maternal sleep-disordered breathing during pregnancy and offspring growth and adiposity in the first 3 years of life. Sci Rep. 2020;10(1):13979. https://doi.org/10.1038/s41598-020-70911-4.
6. Bendor CD, Bardugo A, Rotem RS, et al. Glucose Intolerance in Pregnancy and Offspring Obesity in Late Adolescence. Diabetes Care. 2022;45(7):1540–8. https://doi.org/10.2337/dc21-2634. PMID: 35670776.
7. Miranda RA, Silva BS, de Moura EG, Lisboa PC. Pesticides as endocrine disruptors: programming for obesity and diabetes. Endocrine. 2023;79(3):437–47. https://doi.org/10.1007/s12020-022-03229-y.
8. Sferruzzi-Perri AN, Vaughan OR, Forhead AJ, Fowden AL. Hormonal and nutritional drivers of intrauterine growth. Curr Opin Clin Nutr Metab Care. 2013;16(3):298–309. https://doi.org/10.1097/MCO.0b013e32835e3643.
9. Andersen SL, Olsen J, Laurberg P. Foetal programming by maternal thyroid disease. Clin Endocrinol (Oxf). 2015;83(6):751–8. https://doi.org/10.1111/cen.12744.
10. Eke AC, Saccone G, Berghella V. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and risk of preterm birth: A systematic review and meta-analysis. BJOG. 2016;123:1900–7.
11. Levy M, Kovo M, Miremberg H, et al. Maternal use of selective serotonin reuptake inhibitors (SSRI) during pregnancy-neonatal outcomes in correlation with placental histopathology. J Perinatol. 2020;40(7):1017–24. https://doi.org/10.1038/s41372-020-0598-0.
12. Woody CA, Ferrari AJ, Siskind DJ, Whiteford HA, Harris MG. A systematic review and meta-regression of the prevalence and incidence of perinatal depression. J Affect Disord. 2017;219:86–92. https://doi.org/10.1016/j.jad.2017.05.003.
13. Leonard BE. SSRI differentiation: Pharmacology and pharmacokinetics. Hum Psychopharmacol. 1995;10 Suppl 3(S3):S149–58. https://doi.org/10.1002/hup.470100903.14.
14. Molenaar NM, Houtman D, Bijma HH, et al. Dose-effect of maternal serotonin reuptake inhibitor use during pregnancy on birth outcomes: A prospective cohort study. J Affect Disord. 2020;267:57–62. https://doi.org/10.1016/j.jad.2020.02.003.
15. Dubovicky M, Belovicova K, Csatlosova K, Bogi E. Risks of using SSRI / SNRI antidepressants during pregnancy and lactation. Interdiscip Toxicol. 2017;10(1):30–4. https://doi.org/10.1515/intox-2017-0004.
16. Domingues RR, Fricke HP, Sheftel CM, et al. Effect of Low and High Doses of Two Selective Serotonin Reuptake Inhibitors on Pregnancy Outcomes and Neonatal Mortality. Toxics. 2022;10(1):11. https://doi.org/10.3390/toxics10010011.
17. Ornoy A, Koren G. Selective serotonin reuptake inhibitors in human pregnancy: on the way to resolving the controversy. Semin Fetal Neonatal Med. 2014;19(3):188–94. https://doi.org/10.1016/j.siny.2013.11.007.
18. Calderon-Margalit R, Qiu C, Ornoy A, Siscovick DS, Williams MA. Risk of preterm delivery and other adverse perinatal outcomes in relation to maternal use of psychotropic medications during pregnancy. Am J Obstet Gynecol. 2009;201(6):579.e1-8. https://doi.org/10.1016/j.ajog.2009.06.061.
19. Zullino S, Simoncini T. Impact of selective serotonin reuptake inhibitors (SSRIs) during pregnancy and lactation: a focus on short and long-term vascular effects. Vascul Pharmacol. 2018;108:74–6. https://doi.org/10.1016/j.vph.2018.05.008.
20. Huybrechts KF, Bateman BT, Palmsten K, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. JAMA. 2015;313(21):2142–51. https://doi.org/10.1001/jama.2015.5605.
21. El Marroun H, Jaddoe VW, Hudziak JJ, et al. Maternal use of selective serotonin reuptake inhibitors, fetal growth, and risk of adverse birth outcomes. Arch Gen Psychiatry. 2012;69(7):706–14. https://doi.org/10.1001/archgenpsychiatry.2011.2333.
22. Davidson S, Prokonov D, Taler M, et al. Effect of exposure to selective serotonin reuptake inhibitors in utero on fetal growth: potential role for the IGF-I and HPA axes. Pediatr Res. 2009;65(2):236–41. https://doi.org/10.1203/PDR.0b013e318193594a.
23. Murphy N, Hume R, van Toor H, et al. The hypothalamic-pituitary-thyroid axis in preterm infants; changes in the first 24 hours of postnatal life. J Clin Endocrinol Metab. 2004;89:2824–31.
24. LaFranchi SH. Approach to the diagnosis and treatment of neonatal hypothyroidism. J Clin Endocrinol Metab. 2011;96:2959–67.
25. Almagor T, Rath S, Nachtigal D, et al. High Prevalence of Hearing Impairment in Primary Congenital Hypothyroidism. Eur Thyroid J. 2021;10(3):215–21. https://doi.org/10.1159/000509775.
26. Edrees H, Song W, Syrowatka A, Simona A, Amato MG, Bates DW. Intelligent Telehealth in Pharmacovigilance: A Future Perspective. Drug Saf. 2022;45(5):449–58. https://doi.org/10.1007/s40264-022-01172-5.
27. Fischer A, Rennert HS, Rennert G. Selective serotonin reuptake inhibitors associated with increased mortality risk in breast cancer patients in Northern Israel. Int J Epidemiol. 2022;51(3):807–16. https://doi.org/10.1093/ije/dyac004.
28. Zdraveska N, Kocova M. Thyroid function and dysfunction in preterm infants-Challenges in evaluation, diagnosis and therapy. Clin Endocrinol (Oxf). 2021;95(4):556–70. https://doi.org/10.1111/cen.14481.
29. American College of Obstetricians and Gynecologists. ACOG Committee opinion no. 548: weight gain during pregnancy. Obstet Gynecol. 2013;121(1):210–2. https://doi.org/10.1097/01.aog.0000425668.87506.4c.
30. Zegers-Hochschild F, Adamson GD, de Mouzon J, et al. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. Hum Reprod. 2009;24(11):2683–7. https://doi.org/10.1093/humrep/dep343.
31. Prevention of Group B Streptococcal Early-Onset Disease in Newborns: ACOG Committee Opinion, Number 797. Obstet Gynecol. 2020;135(2):e51-e72. https://doi.org/10.1097/AOG.0000000000003668.
32. Navti OB, Al-Belushi M, Konje JC. FRCOG. Cytomegalovirus infection in pregnancy - An update. Eur J Obstet Gynecol Reprod Biol. 2021;258:216–22. https://doi.org/10.1016/j.ejogrb.2020.12.006.
33. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982;144(7):768–73. https://doi.org/10.1016/0002-9378(82)90349-0.
34. Chou JH, Roumiantsev S, Singh R. PediTools Electronic Growth Chart Calculators: Applications in Clinical Care, Research, and Quality Improvement. J Med Internet Res. 2020;22(1): e16204. https://doi.org/10.2196/16204.
35. Zhu Z, Cao F, Li X. Epigenetic Programming and Fetal Metabolic Programming. Front Endocrinol (Lausanne). 2019;10:764. https://doi.org/10.3389/fendo.2019.00764.

36. McGill MG, Pokhvisneva I, Clappison AS, et al. Maternal Prenatal Anxiety and the Fetal Origins of Epigenetic Aging. Biol Psychiatry. 2022;91(3):303–12. https://doi.org/10.1016/j.biopsych.2021.07.025.
37. Cao-Lei L, van den Heuvel MI, Huse K, et al. Epigenetic Modifications Associated with Maternal Anxiety during Pregnancy and Children's Behavioral Measures. Cells. 2021;10(9):2421. https://doi.org/10.3390/cells10092421.
38. Sylvester C, Menke M, Gopalan P. Selective Serotonin Reuptake Inhibitors and Fertility: Considerations for Couples Trying to Conceive. Harv Rev Psychiatry. 2019;27(2):108–18. https://doi.org/10.1097/HRP.0000000000000204.
39. Cesta CE, Viktorin A, Olsson H, et al. Depression, anxiety, and antidepressant treatment in women: association with in vitro fertilization outcome. Fertil Steril. 2016;105(6):1594-1602.e3. https://doi.org/10.1016/j.fertnstert.2016.01.036.
40. Carvalho CF, Mattia MMC, da Silva H, et al. Psychotropic medication use among women seeking assisted reproductive technology (ART) therapy: A cross-sectional study. J Affect Disord. 2021;292:386–90. https://doi.org/10.1016/j.jad.2021.05.063.
41. Coussa A, Hasan HA, Barber TM. Impact of contraception and IVF hormones on metabolic, endocrine, and inflammatory status. J Assist Reprod Genet. 2020;37(6):1267–72. https://doi.org/10.1007/s10815-020-01756-z.
42. Sciorio R, Esteves SC. Contemporary Use of ICSI and Epigenetic Risks to Future Generations. J Clin Med. 2022;11(8):2135. https://doi.org/10.3390/jcm11082135.
43. Berger BO, Wolfson C, Reid LD, Strobino DM. Adverse Birth Outcomes Among Women of Advanced Maternal Age With and Without Health Conditions in Maryland. Womens Health Issues. 2021;31(1):40–8. https://doi.org/10.1016/j.whi.2020.08.008.
44. Luo J, Fan C, Luo M, Fang J, Zhou S, Zhang F. Pregnancy complications among nulliparous and multiparous women with advanced maternal age: a community-based prospective cohort study in China. BMC Pregnancy Childbirth. 2020;20(1):581. https://doi.org/10.1186/s12884-020-03284-1.
45. Fay EE, Hitti JE, Delgado CM, et al. An enhanced recovery after surgery pathway for cesarean delivery decreases hospital stay and cost. Am J Obstet Gynecol. 2019;221(4):349.e1-349.e9. https://doi.org/10.1016/j.ajog.2019.06.041.
46. Zhang T, Brander G, Mantel Ä, et al. Assessment of Cesarean Delivery and Neurodevelopmental and Psychiatric Disorders in the Children of a Population-Based Swedish Birth Cohort. JAMA Netw Open. 2021;4(3):e210837. https://doi.org/10.1001/jamanetworkopen.2021.0837.
47. Chong CYL, Bloomfield FH, O'Sullivan JM. Factors Affecting Gastrointestinal Microbiome Development in Neonates. Nutrients. 2018;10(3):274. https://doi.org/10.3390/nu10030274.
48. Reyman M, van Houten MA, van Baarle D, et al. Impact of delivery mode-associated gut microbiota dynamics on health in the first year of life. Nat Commun. 2019;10(1):4997. https://doi.org/10.1038/s41467-019-13014-7.
49. Paun A, Danska JS. Modulation of type 1 and type 2 diabetes risk by the intestinal microbiome. Pediatr Diabetes. 2016;17(7):469–77. https://doi.org/10.1111/pedi.12424.
50. Turan S, Bereket A, Angaji M, et al. The effect of the mode of delivery on neonatal thyroid function. J Matern Fetal Neonatal Med. 2007;20(6):473–6. https://doi.org/10.1080/14767050701398314.
51. Murphy MSQ, Ducharme R, Hawken S, et al. Exposure to Intrapartum Epidural Analgesia and Risk of Autism Spectrum Disorder in Offspring. JAMA Netw Open. 2022;5(5): e2214273. https://doi.org/10.1001/jamanetworkopen.2022.14273.
52. Keating C, Dawood T, Barton DA, Lambert GW, Tilbrook AJ. Effects of selective serotonin reuptake inhibitor treatment on plasma oxytocin and cortisol in major depressive disorder. BMC Psychiatry. 2013;13:124. https://doi.org/10.1186/1471-244X-13-124.
53. de Jong TR, Veening JG, Olivier B, Waldinger MD. Oxytocin involvement in SSRI-induced delayed ejaculation: a review of animal studies. J Sex Med. 2007;4(1):14–28. https://doi.org/10.1111/j.1743-6109.2006.00394.x.
54. Ren B, Zhu Y. A New Perspective on Thyroid Hormones: Crosstalk with Reproductive Hormones in Females. Int J Mol Sci. 2022;23(5):2708. https://doi.org/10.3390/ijms23052708.
55. Rosen G, Lavie A, Yackobovitch-Gavan M, et al. Congenital Hypothyroidism Can Dictate the Mode of Delivery and Intra-Labor Medication Usage. Thyroid. 2021;31(12):1878–85. https://doi.org/10.1089/thy.2021.0388.
56. Harrison W, Goodman D. Epidemiologic Trends in Neonatal Intensive Care, 2007–2012. JAMA Pediatr. 2015;169(9):855–62. https://doi.org/10.1001/jamapediatrics.2015.1305.
57. Grunberg VA, Geller PA, Bonacquisti A, Patterson CA. NICU infant health severity and family outcomes: a systematic review of assessments and findings in psychosocial research. J Perinatol. 2019;39(2):156–72. https://doi.org/10.1038/s41372-018-0282-9.
58. Tahirkheli NN, Cherry AS, Tackett AP, McCaffree MA, Gillaspy SR. Postpartum depression on the neonatal intensive care unit: current perspectives. Int J Womens Health. 2014;6:975–87. https://doi.org/10.2147/IJWH.S54666.
59. Ryckman KK, Borowski KS, Parikh NI, Saftlas AF. Pregnancy Complications and the Risk of Metabolic Syndrome for the Offspring. Curr Cardiovasc Risk Rep. 2013;7(3):217–23. https://doi.org/10.1007/s12170-013-0308-y.
60. Shuffrey LC, Lucchini M, Morales S, et al. Gestational diabetes mellitus, prenatal maternal depression, and risk for postpartum depression: an Environmental influences on Child Health Outcomes (ECHO) Study. BMC Pregnancy Childbirth. 2022;22(1):758. https://doi.org/10.1186/s12884-022-05049-4.

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