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Reproductive Safety of Trazodone After Maternal Exposure in Early Pregnancy

A Comparative ENTIS Cohort Study

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Abstract:

Purpose/Background: Trazodone is indicated for the treatment of major depressive disorder, but more frequently prescribed off-label at lower doses for insomnia in women of childbearing age. The aim of this study was to assess the risks linked to trazodone exposure during pregnancy for which limited safety data are available.

Methods/Procedures: This multicenter, observational prospective cohort study compared pregnancy outcomes in women exposed to trazodone in early pregnancy against those in a reference group of women exposed to a selective serotonin reuptake inhibitors (SSRIs) between 1996 and 2021.

Findings/Results: The sample included 221 trazodone and 869 SSRI-exposed pregnancies. Exposure to trazodone in the first trimester was not associated with a significant difference in the risk of major congenital anomalies (trazodone [1/169, 0.6%]; SSRI [19/730, 2.6%]; adjusted odds ratio, 0.2; 95% confidence interval, 0.03–1.77). The cumulative incidences of live birth were 61% and 73% in the trazodone and reference group, respectively (25% vs 18% for pregnancy loss and 14% vs 10% for pregnancy termination). Trazodone exposure was not associated with a significantly increased risk of pregnancy termination and pregnancy loss. The rate of small for gestational age infants did not differ between the groups.

Implications/Conclusions: This study did not reveal a significant difference in the risk of major congenital anomalies after first trimester exposure to trazodone, compared with SSRI exposure. Although this study is the largest so far, these results call for confirmation through further studies.

Key Words: trazodone, pregnancy, reproductive safety, teratovigilance

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Trazodone is a triazolopyridine antidepressant chemically unrelated to the other major classes of antidepressants. It is a serotonin transporter inhibitor, a 5-HT_2 receptor antagonist, and a partial 5-HT_{1A} agonist; it also reduces levels of others neurotransmitters such a noradrenaline, dopamine, acetylcholine, and histamine.[1] It is indicated for the treatment of major depressive disorder in adults. Trazodone is also frequently prescribed off-label at lower doses (50–100 mg/d) for insomnia.[2,3] According to a Cochrane systematic review, trazodone is associated with a small improvement of sleep quality, in comparison to placebo,[4] but safety data are lacking for this indication.

Depression and sleep disorders are frequent in women of childbearing age. De novo sleep disorders may also appear or worsen in patients with preexisting condition during pregnancy (such as mood or anxiety disorders). Antenatal insomnia treatment is clinically challenging because criterion standard Cognitive Behavioral Therapy for Insomnia is not widely available or often fail.[5] Anti-H1 sedating drugs are considered first-line choices in pregnant women due to a large and reassuring amount of safety data,[6,7] even if there is a lack of evidence regarding their efficacy in this indication. Thus, trazodone is often used during pregnancy, off-label, for the treatment of insomnia, and the Teratogen Information Service (TIS) receives frequent requests regarding its safety of use during pregnancy (European Network of Teratology Information Services [ENTIS], oral communication, September 2021, data not published).

According to the product labelling, trazodone was not teratogenic when tested in animal studies performed in rats and rabbits.[8,9] Currently available human pregnancy exposure data presented in more detail in the discussion are provided by 3 prospective studies, which collectively describe approximately 200 exposed pregnancies with approximately 170 exposed in the first trimester.[10–12] Although these studies have not identified concerns, the available data are highly limited and insufficient to conclude that trazodone is safe during pregnancy. Larger cohorts are needed to rule out a small increase in the rate of malformation.

The aim of this study was therefore to assess the risks linked to trazodone exposure during pregnancy. The primary objective

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was to prospectively evaluate the risk of major congenital anomalies after the first trimester exposure to trazodone compared with a reference group exposed to sertraline, citalopram, or escitalopram during the first trimester.[13] Secondary objectives were to evaluate other pregnancy outcomes (spontaneous pregnancy losses such as abortions and stillbirths or pregnancy terminations). Neonatal outcomes including preterm births, gestational age (GA) at birth, birth weight, and neonatal transient effects among those exposed late in pregnancy were also assessed as secondary objectives.

MATERIALS AND METHODS

Study Design and Data Set Description

This study is a multicenter, prospective, observational cohort study with one reference group. All participating centers are members of the ENTIS, an organization of services offering expertise on possible risks related to exposure to medications during pregnancy and breastfeeding at an individual level.[14] Standardized protocols were followed for data collection in each center.[15] Methodological details on similar collaborative studies have already been described in the literature.[16]

Data collection was performed at first TIS contact and after the expected date of delivery using standardized questionnaires to/with the patient and/or her health care professional. No medical chart reviews was done. Maternal characteristics including age, tobacco use and alcohol consumption, and medical and obstetric history were collected. Details on drug exposure, including dose, timing of introduction, duration, and concomitant medications were also collected at initial TIS contact. After the expected date of delivery, follow-up was done through a structured mailed questionnaire and/or a structured telephone interview. Information requested for follow-up included pregnancy outcome, GA at delivery, birth weight, birth defects, and neonatal complications. Socioeconomic and educational data were not available.

Exposed and Reference Groups

Eligible patients were pregnant women exposed to trazodone during the first trimester of pregnancy who themselves or whose practitioner contacted 1 of the 7 participating TIS from 1996 to 2021.[14] Only prospectively ascertained patients were included (ie, unknown pregnancy outcome or prenatal pathology at the time of study enrolment). For each pregnancy outcome with trazodone exposure, 4 patients were selected for the selective serotonin reuptake inhibitors (SSRIs) reference group. The reference group was defined as pregnancies exposed during the first trimester of pregnancy to sertraline, citalopram, or escitalopram, randomly selected within the same TIS prospective cohort and in the same contact time frame (±3 years). Sertraline, citalopram, and escitalopram were selected as they are antidepressants that are frequently prescribed. No limit of duration of exposure was defined for both groups. Patients with either trazodone monotherapy or with concomitant medication use during pregnancy were eligible for the study unless there were listed in the teratogenic drugs below. Cases with concomitant antidepressants or mood stabilizer were included. Exclusion criteria for both groups were exposure to known teratogenic drugs (systemic retinoids, any cytotoxic, selected antiepileptic drugs, thalidomide or derivatives, any coumarin derivatives, misoprostol, carbimazole, and methimazole) at any time during pregnancy; exposure to angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, or tetracyclines during the second and third trimester; presence of malignancies, malignancy-related conditions, or pregestational diabetes; and multiple pregnancies. Duplicate cases were excluded. Data sent from different TIS were collected anonymously.

Outcomes

Congenital anomalies were classified by 2 independent coauthors (M.C.A., D.B.) who were blinded to exposure data, using the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) ICD10-BPA classification system updated in December 2020.[17] The estimation of major congenital anomalies was restricted to live births or pregnancy losses with known results after appropriate medical examination (ie, known birth defect outcome). Minor congenital anomalies were not evaluated because they are subject to significant underreporting. Secondary outcomes were the risks of spontaneous pregnancy losses (abortions and stillbirths, at less than or more than 20 weeks of GA, respectively) and pregnancy terminations. Neonatal outcomes such as preterm births, GA at birth, and birth weight were also analyzed. Gestational age at birth, birth weight, small for GA (SGA) neonates, and observations on neonatal complications/symptoms were compared. Neonatal complications included the description of any symptoms reported at birth; neonatal withdrawal symptoms included the presence of symptoms such as jitteriness, feeding problems, respiratory distress, and or hypoglycemia at birth. Results from validated scales were not available, nor information from medical charts to confirm neonatal withdrawal symptoms. The potential role of period of exposure during pregnancy was explored.

Statistical Analysis

Crude major congenital anomaly risks were calculated by dividing the number of infants or fetuses with congenital anomalies by the number of all live-born infants plus the number of spontaneous abortions, stillbirths, and terminated pregnancies with known congenital anomalies.[14] The association between trazodone exposure and the risk of major congenital anomalies was evaluated using multivariate logistic regression analysis to estimate an odds ratio (OR) with 95% confidence interval (CI).[14] Significant imbalances between the trazodone and SSRI groups were evaluated in the multivariate analysis.

Pregnancy terminations (elective nonmedical terminations of pregnancy [ETOP] or medical terminations of pregnancy [MTOP]) and spontaneous pregnancy losses (spontaneous abortions or stillbirths) were considered as competing risks for pregnancy, and their frequency was represented by cumulative incidence functions.[18,19] In this analysis, women were considered to be at risk for one of these outcomes from GA at the TIS contact, which allows to adjust the analysis for the fact that the GA at TIS contact was not independent of the outcome (a pregnancy termination being, eg, not possible at an advanced GA). Cases with missing GA at pregnancy outcome or at TIS contact were thus excluded from the cumulative incidence analysis. The estimation of cumulative incidence of pregnancy outcome was stabilized for delayed entries (left censoring) using a postpone method, with a cutoff number of women at risk of $n_{min} = 10$, as already described for similar studies.[19,20] To account for any variation in GA at enrolment between the 2 groups, cause-specific Cox proportional hazards models were used to assess the association of the exposure with overall risk of pregnancy loss. To control for potential confounding factors, important imbalances between both groups were considered in the hazards models.

Small for GA was defined as a birthweight smaller than percentile 10 according to World Health Organization infant sex-specific growth charts.[21] Statistical analyses were performed with R (version 3.2.1) and STATA version 9.2 (Stata Corp, College Station, TX).[14,18]

Missing values for tobacco use, alcohol consumption, and folate substitution were coded as an additional category. A sensitivity analysis was performed for variables with more than 20% of

missing values. Pregnant women considered lost to follow-up were not included in the analysis.

The study protocol was approved by the ENTIS scientific committee. In most participating centers, this observational cohort study did not require ethics committee approval; otherwise, ethics committee approval was obtained from appropriate authorities.

RESULTS

This study included 221 women exposed to trazodone in the first trimester of pregnancy compared with a reference group of 869 women exposed to SSRI (sertraline, citalopram, or escitalopram).

MATERNAL CHARACTERISTICS

Maternal characteristics including obstetric and medical conditions are summarized in Table 1. The median maternal age was similar in both groups. Maternal characteristics and the qualification of the caller (patient or health care professional) at initial TIS contact were similar between groups. A higher proportion of women exposed to trazodone reported tobacco use (30.5% vs 17%). Previous spontaneous abortions were reported more frequently in the group of women exposed to trazodone (30.3% vs 19.8%). This was not influenced by any difference in number of previous pregnancies (64.6% vs 62.6%). Alcohol consumption during pregnancy, GA at initial contact, and number of previous ETOP were similar in both groups.

Medical conditions are detailed in Table 1 and were reported for 78% and 82% of women for the trazodone and the SSRI group, respectively. Sleep disorders and bipolar disorders were more frequently reported in the trazodone-exposed group, whereas anxiety disorders were more frequent in the SSRI-exposed group. Thyroid disorders were more frequent in the trazodone group. Hypothyroidism was reported for all of the cases; ongoing levothyroxine was reported in all (n = 12/12) and 56% (n = 10/18) of cases in the trazodone and SSRI group, respectively.

DRUG EXPOSURE

The median daily trazodone dose was 100 mg (interquartile range [IQR], 50–150 mg). It was started before pregnancy in 88.7% of women (n = 196) and stopped at a median GA of 15 weeks (IQR, 6–40). Trazodone was started during pregnancy in 8.1% of women (n = 18), and data were missing for 3.2% (7 patients). The median duration of trazodone treatment during pregnancy was 14 weeks (IQR, 6–40). Trazodone was continued until the end of pregnancy in 40% (89 patients).

In the SSRI reference group, sertraline (n = 322) was the most commonly used drug, followed by escitalopram (n = 291) and citalopram (n = 256). Selective serotonin reuptake inhibitor therapy was started before pregnancy in 84.6% (n = 735) of women and stopped at a median GA of 38 weeks (IQR, 10–40). Selective serotonin reuptake inhibitor was started during pregnancy in 10.9% (n = 95), and data were missing for 4.5% (39 patients). The median duration of SSRI therapy was 37 weeks (IQR, 9–40). Selective serotonin reuptake inhibitor was ongoing until the end of pregnancy in 60% (521 patients).

In the trazodone group, 11% of women were on monotherapy, 55% of the women reported concomitant use of another antidepressant

TABLE 1. Maternal Characteristics and Indication for Antidepressant Use

Characteristics	Trazodone (n = 221)	SSRI (n = 869)
Maternal age (y), median (IQR) (n_t; n_{SSRI} = 220; 857)	33 (29–37)	33 (28–36)
Tobacco use, n (%) (n_t; n_{SSRI} = 187; 766)	57 (30.5)	130 (17.0)
Alcohol consumption, n (%) (n_t; n_{SSRI} = 152; 610)	12 (7.9)	34 (5.6)
GA at initial contact (wk), median (IQR) (n_t; n_{SSRI} = 220; 868)	8 (5–12)	7 (5–11)
Previous pregnancies, n (%) (n_t; n_{SSRI} = 195; 751)		
0	69 (35.4)	281 (37.4)
1	59 (30.3)	203 (27.0)
≥2	67 (34.4)	267 (35.6)
Previous spontaneous abortions, n (%) (n_t; n_{SSRI} = 142; 587)		
0	99 (69.7)	471 (80.2)
1	32 (22.5)	87 (14.8)
≥2	11 (7.8)	29 (4.9)
Previous ETOP, n (%) (n_t; n_{SSRI} = 145; 581)		
0	119 (82.1)	514 (88.5)
≥1	26 (17.9)	67 (11.5)
Medical conditions, n (%) (n_t; n_{SSRI} = 172; 709)		
Psychiatric disorder	156 (90.7)	637 (89.8)
Depression	91 (52.9)	354 (50.4)
Anxiety	45 (26.2)	242 (34.5)
Bipolar disorder	13 (7.6)	20 (2.9)
Other psychiatric condition	38 (22.1)	138 (19.7)
Sleep disorder	35 (20.4)	15 (2.1)
Epilepsy	0 (0)	4 (0.6)
Hypertension	3 (1.7)	3 (0.4)
Thyroid disorder	12 (7.0)	18 (2.6)
Other	39 (22.7)	130 (18.5)

n_t indicates number for trazodone-exposed group; n_{SSRI}, number for SSRI-exposed group.

or psychostimulant, 43% of a sedative, and 11% of an antiepileptic drug. In the SSRI group, 37% of women were on monotherapy. Concomitant drug use was less frequent: 12% of women reported the use of another antidepressant drug, 28% of sedatives, and 3% of antiepileptic drug.

The rate of loss to follow-up was 43% in the trazodone group (n = 260/610). The rate of loss to follow-up was 33% in Lausanne, Switzerland (n = 54/162); 26% in Bergamo, Italy (n = 7/27); 68% in the United Kingdom (n = 100/147); 37% (n = 77/208) in Jerusalem, Israel; 40% in Zerifin, Israel (n = 6/15); 42% in Geneva, Switzerland (n = 13/31); and 15% (n = 3/20) in Florence, Italy. The rate of loss to follow-up was 62% in the SSRI group (n = 2249/3606). The rate of loss to follow-up was 44% in Lausanne, Switzerland (n = 154/364); 12% in Bergamo, Italy (n = 8/68); 68% in the United Kingdom (n = 1576/2302); 38% (n = 170/450) in Jerusalem, Israel; 80% in Geneva, Switzerland (n = 251/313); and 83% in Florence, Italy (n = 90/109). Loss to follow-up rate was not available for Zerifin in Israel, because follow-up was not systematically performed for women exposed to SSRIs.

PREGNANCY OUTCOMES

The proportions of offspring with major congenital anomalies in the trazodone- and SSRI-exposed pregnancies are reported in Table 2. The rate of major congenital anomalies excluding genetic or chromosomal anomalies was not statistically different between the trazodone and the SSRI group (0.6% vs 2.6%; unadjusted OR, 0.2; 95% CI, 0.03–1.68; $P = 0.15$). The exclusion of anomalies known of genetic or chromosomal origin, and thus not imputable to drug exposure, is standard practice; there were 1 and 4 such cases in the trazodone and the SSRI group, respectively. Adjustment for potential confounding factors (tobacco use, previous spontaneous abortion, previous ETOP) did not modify the odds ratio (0.2; 95% CI, 0.03–1.94; $P = 0.18$). Details on reported congenital anomalies, concomitant medications, and maternal conditions are available in Table 3. Only one major congenital anomaly was reported in the trazodone-exposed group (kidney malformation with bladder agenesis) in a woman taking 200 mg/d of trazodone and 60 mg/d of citalopram for a recurrent depressive disorder. In the SSRI reference group, 19/730 children with major malformations were observed (including 7 cardiovascular malformations).

A total of 1040 women have been included in the cumulative incidence analysis (including 214 trazodone-exposed pregnancies and 826 SSRI-exposed ones). The crude proportions of live births, pregnancy losses (spontaneous abortions and stillbirths), and pregnancy terminations (ETOP or MTOP) were respectively of 77%, 14%, and 10% in the trazodone group and of 84%, 11%, and 6% in the reference group. Cumulative incidence estimates for live births, pregnancy losses, and pregnancy termination were of 61%, 25%, and 14%, respectively, in the trazodone group (and of 73%, 18%, and 10% in the reference group) (Fig. 1, Table 4).

In the corresponding (unadjusted) Cox proportional cause-specific hazards models, an increased risk of TOP (HR, 1.90; 95% CI, 1.14–3.17; $P = 0.01$) and no increased risk of pregnancy losses (HR, 1.44; 95% CI, 0.95–2.20; $P = 0.09$) was observed in the trazodone group (Table 4). Once adjusted for potential confounders, however, these increased risks were no more statistically significant for both outcomes (HR_{adj}, 1.43; 95% CI, 0.92–2.21; $P = 0.11$ for pregnancy loss; HR_{adj}, 1.57; 95% CI, 0.91–2.69; $P = 0.1$ for TOP).

The rate of preterm infants was higher in the trazodone group (n = 22, 13.5%) compared with the SSRI group (n = 57, 8.3%, $P = 0.05$). Birthweight as well as the rate of SGA patients did not differ between the groups. Details for other pregnancy and neonatal outcomes are presented in Table 5.

In the trazodone group, 11 (21%) of 53 term neonates that were exposed until delivery presented neonatal complications. Complications reported were respiratory problems (n = 3), withdrawal symptoms (n = 1), hypoglycemia (n = 2), asphyxia (n = 1), or unspecified (n = 4). Nine (16%) were exposed to at least 1 other psychotropic comedication. Median trazodone dose was 100 mg (IQR, 75–175 mg).

In the SSRI group, 59 (17%) of 343 term neonates that were exposed to one SSRI until delivery presented neonatal complications. Complications reported were respiratory problems (n = 17), withdrawal symptoms (n = 13), hypoglycemia (n = 9), suspicion of neonatal infection (n = 3), jaundice (n = 4), meconium aspiration (n = 4), hypothermia (n = 1), hypotonia (n = 2), thrombocytopenia (n = 1), asphyxia (n = 1), pneumothorax (n = 1), or unspecified (n = 3).

Rates of neonatal complications were similar if trazodone or an SSRI was continued until delivery for term neonates (trazodone 21% vs SSRI 17%).

DISCUSSION

This observational prospective multicenter study is the largest comparative evaluation of reproductive safety of trazodone published so far. A statistically significant difference in the rate

TABLE 2. Risk of Birth Defects in Pregnancies Exposed to Trazodone During the First Trimester Compared With the SSRI-Exposed Reference Group

	Trazodone	SSRI	OR_{adj} (95% CI)	*P*
Major congenital anomalies excluding chromosomal or genetic, n (%)*	1/169 (0.6)	19/730 (2.6)	0.2 (0.03–1.94)	0.18
Major birth defects—subgroups of anomalies				
Congenital anomalies of kidney, n	1	1		
Congenital heart defects, n		7		
Nervous system anomalies, n		2		
Genital anomaly, n		3		
Limb anomaly, n		4		
Gastrointestinal anomalies, n		1		
Orofacial clefts, n		1		
Other anomalies, n		3		

*Including live births, stillbirths, and anomalies in elective pregnancies termination or spontaneous abortions: 1 therapeutic termination in the trazodone group and 2 in the SSRI group.

TABLE 3. Major Birth Defects in Trazodone and SSRI-Exposed Pregnancies, Concomitant Medication, and Maternal Condition

	Outcome	Exposure[†]	Concomitant Medication	Maternal Condition
Major birth defects in trazodone-exposed pregnancies				
Kidney malformation with bladder agenesis	TOP	0–5	Citalopram (0–8)	Depression
Major birth defects in SSRI-exposed pregnancies				
Citalopram				
Spina bifida	Live birth	0–38	(No folate)	Anxiety disorder, anemia
Hexadactylia	Live birth	0–40	Alprazolam (0–40), quetiapine (0–7), alcohol (1 L vodka/d), tobacco	Substance abuse (alcohol and tobacco)
Microcephaly, scalp cutis aplasia	Live birth	9-?	—	Depression, anxiety disorder
Atrioventricular canal defect (fetal hydrops)	TOP	0–5	Minocycline (0–5)	Mood disorder, acne
Patent or persistent foramen ovale, ventricular septal defect	Live birth	?	Quetiapine*	Depression, ADHD
Escitalopram				
Hypospadias	Live birth	0-?	—	Anxiety disorder
Interrupted aortic arch (type A), coarctation of the aorta, ventricles asymmetry, ventricular septal defect	TOP	0–5	—	Unknown
Ventricular septal defect	Live birth	0–40	Azelaic acid,* dipyrone*	Anxiety disorder, allergy
Polydactyly (bilateral)	Live birth	0–40	Paracetamol (30-?)	Anxiety disorder
Hypospadias	Live birth	0–40	—	Anxiety disorder
Congenital constriction bands	Live birth	3–34	Agomelatine (1–3), zolpidem (30–?), acetylsalicylic acid,* progesterone,* flurazepam (0–30)	Depression, sleep disorder, tobacco use
Esophageal atresia	Live birth	0–38	Alprazolam (0–10)	Depression
Hypoplastic left heart	Live birth	0–40	Enoxaparin (?–40), sumatriptan* on demand 1–2×/wk, acetylsalicylic acid (?–30)	Unknown
Sertraline				
Cleft palate (soft)	Live birth	0–40	Mirtazapine* (ongoing at 8), sulpiride,* alprazolam*	Unknown
Polydactyly	Live birth	0–8	—	Depression, anxiety disorder
Pierre Robin sequence	Live birth	0-?	Quetiapine (0–?)	Unknown
Ebstein anomaly	Live birth	?	Lamotrigine (0–37), quetiapine on demand*	Epilepsy
Tricuspid insufficiency	Live birth	0–38	—	Anxiety disorder
Hypospadias, polydactyly, unspecified polycystic kidney	Live birth	0–40	Venlafaxine (0–14), ondansetron (23–38), nitrofurantoin (24–25), metoclopramide (0–12), cyclizine prochlorperazine*	Anxiety disorder

*Unknown time of exposure.

[†]Weeks of gestation.

of major congenital anomalies between the trazodone-exposed and SSRI-exposed groups was not observed. Our results support findings from already published studies that found no increased risk for major congenital anomalies after exposure to trazodone or nefazodone during pregnancy.[10–12] In the surveillance study of Michigan Medicaid recipients conducted between 1985 and 1992, 100 newborns had been exposed to trazodone during the first trimester, with 1 (1%) major congenital anomaly reported.[22] A prospective study of 147 exposures to trazodone (n = 58) or the related substance nefazodone (n = 89) during the first trimester showed no significant increase in the risk of major congenital anomalies.[10] Another prospective study including 13 exposures to trazodone did not report cases of major congenital anomalies.[12,23] In addition, several dozen other exposures (registries, case reports) did not suggest an increase in the risk of congenital anomalies.[11] There were no complications in 18 neonates whose mothers had been treated for insomnia beginning at weeks 26 to 32 with trazodone in a prospective single-blind controlled study.[24] Available data are, however, insufficient to conclude that this drug is safe during pregnancy.

The rate of major congenital anomalies observed after first trimester exposure to trazodone was actually lower than the baseline risk of 3% to 5% found in the general population.[25,26] The rate of major congenital anomalies for the SSRI-exposed group was within the expected baseline risk. It is worth to recall here that an overall increase of congenital anomalies, in particular cardiovascular anomalies, although of limited magnitude, has been reported in several studies for SSRIs.[13] The limited study sample size of 221 women allows ruling out a 2-fold increase in major congenital anomalies after trazodone therapy.[16]

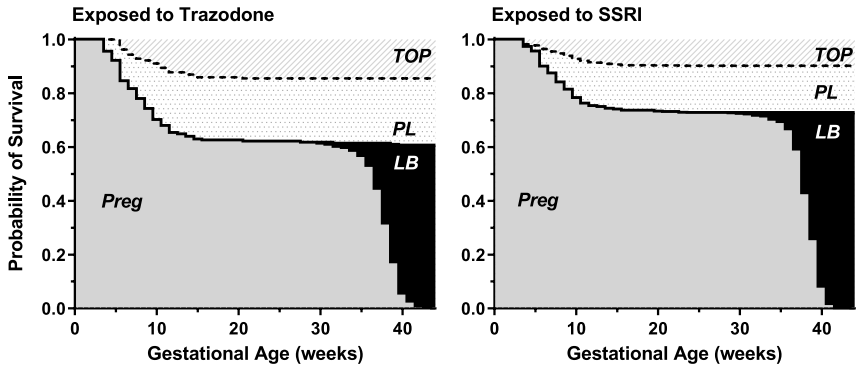

FIGURE 1. Cumulative incidences of pregnancy outcomes with livebirth (LB), pregnancy losses (PL), and pregnancy termination (TOP) in women exposed to trazodone (n = 214) versus SSRI-exposed women (n = 826).

Small increases in risk for rare specific defects would not be detected in our study.

The unique major congenital anomaly reported in the trazodone group, a kidney malformation with bladder agenesis, does not allow discussing any cluster of malformation. No autopsy report was retrieved for this case to confirm the diagnosis of bladder agenesis. Long-term follow-up was not available to assess a potential neurodevelopmental impact of trazodone. Observational studies with longer follow-up should be designed to answer this question.

There was a higher crude rate of ETOPs in the trazodone-exposed group. In the Cox adjusted model, trazodone exposure was, however, not associated with a statistically significant increased risk for ETOPs. A higher rate of unplanned pregnancies in women exposed to trazodone and psychiatric underlying maternal conditions, with more frequent anxiety and bipolar disorders in the trazodone group, may explain these results. A trend for a higher rate of pregnancy losses in the trazodone-exposed group can be observed in Figure 1. However, no statistically significant difference was found in the Cox adjusted models. Crude rates (13.6% vs 10.2%), which should be interpreted with caution, were similar and lied within normal background ranges for spontaneous abortions.[27] Gestational age at first TIS contact were similar in both groups.

The rate of preterm infants was higher in the trazodone group, and most of preterm deliveries occurred during the 35th and 36th weeks of gestation. The median GA at birth was, therefore, also smaller for trazodone-exposed women. Maternal conditions and tobacco use were more frequent in the trazodone group, and may have represented risk factors for preterm delivery.[28] Birthweight was however similar in both groups, without difference in the rate of SGA newborns for newborns where information was available. Neonatal outcomes (including withdrawal symptoms, hypoglycemia, and respiratory distress) were similar for term neonates exposed to either trazodone or SSRI until delivery. Such neonatal complications were reported in a significant proportion of cases but should be interpreted with caution because concomitant maternal medications were ongoing in many cases. The absence of detailed chart reviews to carefully evaluate neonatal symptoms is a limitation for the interpretation these results. Furthermore, women in the trazodone group were more frequently on concomitant psychotropic drugs. Exposed neonates to any psychotropic drugs should be carefully monitored for withdrawal or toxicity symptoms after birth.

The strengths and limitations of collaborative ENTIS studies have already been discussed in the literature.[15] The reference group with SSRI-exposed women sharing similar medical conditions is a strength. More severe psychiatric disease in the trazodone group and lower doses of trazodone used for insomnia (than for depression) however limit the comparison with SSRI-exposed women. Although this is the largest study on trazodone exposure in the first trimester of pregnancy, the sample size is still too small and the length of follow-up too short to draw definitive conclusions on the safety of trazodone use during pregnancy. The controversial increased risk for major birth anomalies of SSRIs is another limitation of the study and might also contribute to explain that our reference group had a slightly although not significantly higher risk of congenital anomalies than in the trazodone group. We did not include a healthy reference group to compare pregnancy outcomes, and the observed rate of lost to follow-up cases was high in the trazodone group (43%) and very high in the SSRI group (62%), which are limitations. Exclusion of any methodological bias is not possible, but prospective documentation of exposure data with similar procedures across cohorts minimizes possible biases or outcome misclassification.[18] Overrepresentation of middle- to high-level educated women in TIS cohorts[29] prevents from generalizing these results to the general population. Such results offer some reassurance and are, however, of importance for women experiencing insomnia and/or depression during childbearing age and pregnancy.

In conclusion, overall pregnancy outcomes including the risk of major congenital anomalies and spontaneous abortion after trazodone

TABLE 4. Pregnancy Outcomes—Cox Analysis

	Trazodone vs SSRI Subjects				Trazodone vs SSRI (Crude Rates)	
	HR (95% CI)	*P*	HR_{adj} (95% CI)*	*P*	n (%)	
Pregnancy loss (spontaneous abortions, stillbirths)	1.44 (0.95–2.20)	0.087	1.43 (0.92–2.21)	0.110	29 (13.6)	88 (10.7)
Pregnancy termination (elective or medical)	1.90 (1.14–3.17)	0.014	1.57 (0.91–2.69)	0.100	21 (9.8)	48 (5.8)

*Adjusted for maternal age, tobacco use, folate intake, past abortion or termination history, country of TIS.

TABLE 5. Pregnancy Outcomes

	Trazodone	SSRI
Live-born infants, n (%)	164 (74.2)	722 (83.1)
Elective termination of pregnancy, n (%)	22 (10)	50 (5.8)
Medical termination of pregnancy, n (%)	1 (0.5)*	3 (0.4)†
Spontaneous abortion, n	30	89
Stillbirth, n (%)	4 (1.8)	5 (0.6)
Preterm delivery, n (%)	22 (13.5)	57 (8.3)
GA at birth (wk), median (IQR) (n_t = 164; n_{SSRI} = 691)	39 (37–40)	39 (38–40)
Birthweight (g), median (IQR) (n_t = 155; n_{SSRI} = 675)	3125 (2800–3500)	3162 (2880–3500)
Small for gestational age, n (%)	22 (14.2)	118 (18.2)

*Reason for medical termination of pregnancy: 1 congenital anomaly.
†Reason for medical termination of pregnancy: 2 congenital anomalies, 1 genetic.

exposure were similar to that of the reference group exposed to SSRI. Trazodone seems as a therapeutic option for treatment of sleep disorders during pregnancy; however, further studies are still needed for confirmation of trazodone reproductive safety.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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The data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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