Teratology Information, Training and Research Center) for a risk assessment regarding TCC exposure during pregnancy.

Methods: A search through all prospectively recorded referrals with an exposure to TCC during pregnancy between the years 2009–2014 in our records retrieved the data of forty-eight pregnant women. Information regarding pregnancy outcomes was collected through structured telephone interviews with mothers/families.

Results: Of 48 pregnancies, the majority of the exposures (91.7%) occurred during the first trimester with a mean maternal gestational age at admission of 8.3 ± 3.3 weeks. The median daily dose of TCC was 8 mg/d and the duration of exposure varied between 1 and 49 days. The route of administration was oral in 32, intramuscular in 11 and was unknown in 5 of the pregnant women respectively. Of the 43 pregnancies with known outcomes, 32 (74.4%) were live births, 4 (9.3%) were spontaneous abortions and 7 (16.3%) were elective abortions. There were 2 major (6.4%) (a cleft lip with palate and a bilateral hip dislocation) and 1 minor (3.1%) (vesicoureteral-renal reflux) congenital malformations and twenty-nine (90.6%) normal outcomes in live births. Among the infants with normal outcomes at birth, one infant was diagnosed with unilateral hydronephrosis at 6 months and another infant with immunodeficiency 1.5 years after the delivery, respectively.

Conclusions: The collective evaluation with our results with the previously reported case series, which included the outcomes of 41 and 18 pregnancies following TCC exposure, suggest that inadvertent exposure to TCC during early pregnancy is unlikely to be associated with a substantial embryotoxicity. Although these results may offer some value to clinicians for counseling the pregnant women with inadvertent TCC exposure, the lack of a control group and small number of cases preclude further conclusions. We suggest the continuation of the restriction of TCC use in pregnant women and increasing the surveillance regarding TCC exposure during pregnancy to ascertain further outcomes.

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Opipramol for antidepressant therapy in early pregnancy

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Introduction: The tricyclic antidepressant opipramol is used in Europe for more than 50 years. Nevertheless references on possible reproductive effects of opipramol are missing. The present study aimed to compare outcomes of pregnancies exposed to opipramol with no or non-teratogenic medication during first trimester of pregnancy.

Methods: In a prospective follow-up study we collected data of pregnancy outcomes after medication with opipramol ($n = 243$) between 1989 and 2015. Our Teratology Information Service (TIS) was contacted by physicians and patients after exposure to opipramol in the first trimester. We compared the results with a control group ($n = 901$) of our TIS in the same interval, which was not or not severely exposed. Statistical evaluation was performed by Fisher's Exact Test. The gestational age at call did not differ between both groups (day 49 vs day 51; $p = 0.80$), the maternal age however was higher in the exposed group (33 years vs 30 years; $p < 0.001$).

Results: After treatment with opipramol 22 patients (22/243 = 9.1%) preferred early termination of pregnancy. The incidence of elective terminations of pregnancy was higher ($p = 0.00002$) after therapy with opipramol than in the control group (22/901 = 2.4%). The other 221 documented pregnancies ended with spontaneous abortions in 33 cases and ongoing pregnancies in 188 cases. The rate of spontaneous abortions (33/221 = 14.9%) did not differ significantly from the control group (89/879 = 10.1%, $p = 0.054$). 14 congenital anomalies were reported after intrauterine exposure to opipramol in early pregnancy: severe developmental delay ($n = 3$), cleft lip ($n = 2$), hydronephrosis ($n = 2$), choanal atresia, ingunial hernia, corpus callosum agenesis, trisomy 18 ($n = 3$), trisomy 21. After exclusion of chromosomal aberrations in both groups the overall rate of congenital anomalies was not significantly increased when patients had been treated with opipramol in early pregnancy (10/184 = 5.4% vs 27/787 = 3.4%; relative risk 1.58; 95% confidence interval 0.73, 3.34). A consistent pattern of anomalies could not be confirmed.

Conclusions: Our prospective controlled follow-up study does not support the assumption of a teratogenic effect of opipramol.

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Collaborative ENTIS study of the fetal effects of maternal varenicline use in pregnancy

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Introduction: Varenicline (ATC code: N07BA03) is a smoking cessation aid for which limited published pregnancy safety data currently exist [1].

Methods: This multicentre prospective observational comparative cohort study was performed using data collected from eight member organizations of the ENTIS network, and included pregnancies occurring between 2001 and 2014. The study sample consisted of eighty-nine varenicline exposed pregnancies and two matched comparator groups consisting of 267 non-teratogen exposed (NTE) controls and 78 exposed to nicotine replacement therapy or bupropion (NRT/B) for smoking cessation. Crude rates of any, major and minor non-genetic congenital malformations were compared between exposed and comparator groups using exact methods. We also estimated hazards ratios for live birth, spontaneous abortion, elective termination and intrauterine fetal

death/stillbirth using time-dependent Cox proportional hazards models.

Results: For all exposed pregnancies, varenicline use occurred in the first trimester only, with a considerable proportion discontinuing use early in pregnancy (72.1% <6 gestational weeks). No significant increased risk of overall (i. vs. NTE: OR 1.54, 95%CI 0.508 to 4.25, ii. vs. NRT/B: OR 1.02, 95%CI 0.280 to 3.87), major (i. OR 3.03, 95%CI 0.217 to 42.4, ii. OR 1.76, 95%CI 0.090 to 106), or minor (i. OR 1.26, 95%CI 0.339 to 4.00, ii. OR 0.87, 95%CI 0.192 to 3.94) non-genetic congenital malformation was observed following first trimester varenicline exposure. No significant increase in spontaneous abortion or intrauterine fetal death/stillbirth was identified between exposed and comparator groups. A statistically significant increase in the rate of elective termination was identified following maternal varenicline use in comparison with NTE controls (aHR 4.57, 95%CI 1.66 to 12.6), although this was not replicated in the comparison with NRT/B exposed controls (aHR 1.65, 95%CI 0.564 to 4.83).

Discussion: No evidence of an increased risk of congenital malformation was identified in this study, but the findings are limited by early therapy discontinuation and the small sample size. In view of these limitations and the lack of additional published safety data, routine use of varenicline as a smoking cessation aid in pregnancy cannot currently be recommended.

Reference

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The necessity of therapeutic levetiracetam (Keppra®) monitoring during pregnancy: A prospective study

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Introduction: Levetiracetam (Keppra®) is a relatively new anti-epileptic drug (AED), indicated as an adjunctive therapy for partial-onset seizures and primary generalized tonic-clonic seizures in adults and children. However, information about the influence of altered pharmacokinetics during pregnancy on levetiracetam's dose, serum concentration and clinical efficacy is still limited. This study aims to describe the relation between certain parameters of pregnant women and levetiracetam's blood levels in different stages of pregnancy.

Methods: Pregnant women treated with levetiracetam for epilepsy from neurology clinics in 3 medical centers (Sourasky, Sheba, Assaf Harofeh) were followed in this study. Through blood samples were obtained (therapeutic range: 10–37 mg/L) in different stages of pregnancy, while sampling frequency for each woman was decided by the neurologist. Levetiracetam blood level, dose, pregnancy week, and seizure occurrence were recorded. Blood samples were drawn at our TIS, and measured by HPLC in our biochemistry department. Univariate and multivariate linear mixed models were used to evaluate changes in blood level before and during pregnancy. The multivariate model included dose and age. A two-tailed $p < 0.05$ was considered statistically significant. Analysis were performed with SPSS (ver. 22). The study was approved by the IRB.

Results: Twenty-eight pregnant women were included in this study. No significant difference was found between blood levels before (22.6 mg/L, 95% CI; 14.9–30.2) and during pregnancy (I: 13.9, 95% CI; 8.7–19.1, II: 18.8, 95% CI; 14.3–23.4 and III: 16.7, 95% CI; 11.3–22.1). However, when adjusting for dose, a significant difference was found ($p = 0.005$). When blood level was adjusted according to pregnancy week and dose, a decrease of 0.26 mg/L (95% CI; 0.07–0.46) in blood level per week was observed. When the dose was adjusted according to pregnancy week, an increase of 36.7 mg of levetiracetam dose (95% CI; 16.7–56.7) per week was observed ($p < 0.001$). No significant association was found between seizure frequency and the dose, age and pregnancy trimester or week.

Conclusions: Levetiracetam blood levels are prone to decrease during pregnancy as opposed to pre-pregnancy state. When levetiracetam's blood levels fall below the therapeutic range, as may happen during pregnancy, there may be a higher risk for seizures. Therefore, monitoring of levetiracetam blood levels during pregnancy is essential in order to increase the dose accordingly, thus maintaining therapeutic blood levels and decreasing the risk for seizures.

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Anogenital distance as a marker of reproductive toxicity

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Background: Increasing evidence suggests that exposures to man-made chemicals found in commonly used products, such as personal care products, the lining of cans used for foodstuffs and others, are endocrine disruptors. Further evidence suggests that endocrine disruptors are associated with adverse child development, especially neurodevelopment, development of the reproductive system and obesity. Here, we report results examining associations between exposure to polybrominated diethyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) and anogenital distance (AGD), a measure influenced by androgen exposure