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Use of tramadol in early pregnancy and congenital malformation risk

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ABSTRACT

Only few studies exist regarding the risk of a teratogenic effect of tramadol when used in early pregnancy. Using the Swedish Medical Birth Register, women (deliveries in 1997–2013) who had reported the use of tramadol in early pregnancy were identified. Maternal characteristics and concomitant drug use were analyzed. Among 1,682,846 women (1,797,678 infants), 1751 (1776 infants) had used tramadol, 96 of the infants had a congenital malformation and 70 of them were relatively severe. The adjusted odds ratio for a relatively severe malformation was 1.33 (95% CI 1.05–1.70). The odds ratios for cardiovascular defects (1.56, 95% CI 1.04–2.29) and for pes equinovarus (3.63, 95% CI 1.61–6.89) were significantly increased. The study suggests a teratogenic effect of tramadol but the risk increase is moderate.

1. Introduction

Many studies have demonstrated the harmful effects on the fetus/child of maternal abuse of opiates or opioids during pregnancy, (*e.g.*, [1,2]) and when taken during the late part of pregnancy neonatal abstinence symptoms are common [3].

Less is known about the effects on the fetus from the use of prescribed opioids as analgesics during early pregnancy. Although some animal data suggest adverse neurodevelopment outcomes due to opiate exposure in early life, clinical data in humans remains insufficient and inconclusive [4,5]. Nevertheless, the few data available for morphine [6] and codeine [7] do not indicate teratogenic properties when used during the first trimester.

Tramadol is a commonly prescribed and centrally acting atypical opioid analgesic. It was registered in Sweden in 1995 but is has been on the European market since the 1970s [8] and it is used for moderate to severe pain. Despite the widely use of the drug little is known about its possible teratogenicity. A review article on tramadol in pregnancy [9] stressed this lack of information when used in early pregnancy but quoted a reassuring conference abstract of a prospective French TIS study [10]. In this 146 tramadol exposed pregnancies and 292 matched controls did not demonstrate a significant difference in malformation rate. This was based on 6 cases in the exposed and 15 in the non-exposed group. To the best of our knowledge no other studies than Bloor et al. [9] has assessed the possible malformation risk when tramadol was used during the first trimester of the pregnancy.

In Sweden the number of prescriptions of tramadol tripled between the years 1999–2011; from 7,914,195 defined daily doses (DDD) to 21,118,870 in the whole population and a similar increase in prescription rate was seen in fertile women, 15–49 years (1,087,536 to 3,390,877 DDD). During the same time the use of dextropropoxyphene declined dramatically [11]. For decades dextropropoxyphene alone or in combination with other analgesics were very common in Sweden. However, due to increased drug abuse and the high toxicity of dextropropoxyphene a policy of restricted prescription was applied by the authorities in 2001, and from 2011 the substance was withdrawn from the market. Based on statistics of analgesic prescription patterns one conclusion is that tramadol seem to have replaced the use of dextropropoxyphene.

The increasing medical use of tramadol and the pharmacological properties of the drug make studies of its possible effect on malformation risk important. The present study presents data from Swedish health registers. For comparison data on other opiates or opioids are given

2. Material and methods

The study was based on the Swedish Medical Birth Register. Since July 1st, 1994 this register contains information on mater-

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Table 1
Risk estimates for specific malformations after maternal use of tramadol in early pregnancy; conditions with at least four cases exposed to tramadol are included.

Malformation	Number with tramadol	Total number	OR/RR	95% CI
Any malformation	96	79127	**1.30**	**1.06–1.69**
Relatively severe malformation	70	52195	**1.33**	**1.05–1.70**
Any cardiovascular defect	26	17117	**1.56**	**1.04–2.29**
Isolated cardiac septum defect	16	8891	**1.78**	**1.02–2.90#**
Pes equinovarus	9	2275	**3.63**	**1.66–6.89#**
Hypospadias	5	5076	0.95	0.31–2.21#
Polydactyly	4	1977	1.77	0.48–4.33#

Odds ratio (OR) or risk ratio (RR marked with #) with 95% confidence interval (95% CI) after adjustment for year of delivery, maternal age, parity, smoking, and BMI. Bold text marks statistical significance.

nal use of drugs in early pregnancy, based on interviews made by midwives at the first antenatal care visit of the pregnant woman, in most cases during weeks 10–12 [12]. The interviews are structured and the records for registration are identical in all prenatal care centers. At the interviews the women were asked which drugs, if any, they had taken since they became pregnant. The midwives wrote down the answers in clear text which subsequently was translated to ATC (Anatomical, Therapeutic, Chemical) codes. The register also contains medical and other information on the women. In the present study, the following information was used: delivery year, maternal age (five-year classes, <20, 20–24 *etc.*), parity (1, 2, 3, ≥4 where 1 means that it is the woman's first delivery), smoking in early pregnancy (unknown, none, <10 cigarettes per day, ≥10 cigarettes per day), pre-pregnancy body mass index (BMI) (unknown, <18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥35), and reported length of a period of unwanted childlessness (in years).

The presence of congenital malformations in the infant was ascertained from multiple sources and all malformation diagnoses are based on ICD codes. The Medical Birth Register contained neonatal diagnoses given by the pediatrician which examined the newborn baby. Major malformations were reported to the Birth Defect Register and could also be identified from discharge diagnoses after hospitalizations in the Patient Register. Information from these sources was linked using the personal identification number of the mother and the child, numbers which are unique for each Swedish resident.

The study investigated the risk of a congenital malformation or a group of congenital malformations in children exposed during early development to tramadol or to other opiates or opioids. Among the latter, opioids used in substitution therapy were not included (methadone and buprenorphine). The presence of malformations among children exposed to the drug was compared with that among unexposed children after adjustment for year of delivery, maternal age and parity, maternal smoking in early pregnancy, and BMI before pregnancy; all factors which affect both the use of tramadol and the risk of a congenital malformation. As the first identified exposure occurred in 1997, the study was restricted to the period 1997–2013 (2013 was the last year with information available).

The analysis was first made for any congenital malformation and was then restricted to "relatively severe malformations" which means that some common and clinically less important malformations with a rather variable registration were excluded. These conditions were preauricular appendix, tongue tie, patent ductus arteriosus in preterm infants (<37 weeks), single umbilical artery, undescended testicle, unstable hip or hip (sub) luxation, and nevus. Some specific malformations were also analyzed, in those cases with the exclusion of infants with a chromosome anomaly. Pes equinovarus was not counted as such when combined with a lower limb reduction or spina bifida.

At the calculation of odds ratios (OR), adjustment was made with Mantel–Haenszel methodology and the approximate 95% confidence interval (95% CI) was estimated with Miettinen's method.

Table 2
Specification of the isolated cardiovascular defects in children exposed to tramadol in early pregnancy.

Cardiac defect	Number
Ventricular septum defect	7
Atrium septum defect	6
Atrium septum defect + stenosis of pulmonary artery + PDA	1
Ventricular and atrial septum defect	3
Stenosis of pulmonary artery	1
Pulmonary valve stenosis	1
Aortic valve stenosis	1
Coarctation of aorta	1
Unspecified cardiac defect	1

When the expected number of malformed children after exposure was less than 10, a risk ratio was instead calculated as the observed number divided with the expected number (adjusted as above) and the 95% CI was based on exact Poisson confidence intervals.

3. Results

Among 1,682,846 women 1751 reported the use of tramadol, 1.04 per 1000. Fig. 1 shows how this rate changed during the observation period from a very low level shortly after the drug was introduced on the Swedish market to a maximum use around 2006 (1.8 per 1000), followed by a clear decline during the remaining period.

There were 1776 infants born to women who had reported use of tramadol in early pregnancy (1,797,678 infants born all together) and 25 were twin deliveries, 1.4%. Table 1 shows risk estimates for some groups of malformations of which all but two reached statistical significance. The cardiovascular defects found are specified in Table 2. If women who reported a period of unwanted childlessness were excluded, the risk estimates increased a little (data not shown), except that for pes equinovarus which decreased slightly (RR = 3.20; 95% CI 1.29–6.59) based on seven exposed cases. Table 3 specifies the different malformations observed after exposure to tramadol, divided into "major" and "minor or uncertain".

Women reporting the use of tramadol differed in many aspects from other women (Table 4). The age dependency was not very strong but a low use was seen in women below 20 years of age and an increased use at age ≥40. The use at parity 2 was marginally low but at higher parity the use increased. There was a strong association with smoking and a weaker one with obesity and with unwanted childlessness. Moreover, there was a significantly excess use of many other drugs by women also taking tramadol: drugs for gastro-esophageal reflux diagnosis (GERD), drugs used for hypertension, oral contraceptives, corticosteroids, antibiotics, NSAIDs, minor analgesics, drugs for migraine, anticonvulsants, sedatives/hypnotics, drugs for asthma, and antihistamines (Table 5). Among these drugs, drugs for hypertension and anticonvulsants are likely to have a teratogenic effect while the evidence of such effect for the other drugs used in excess is weak or absent. Removal from the analysis of women who had