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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

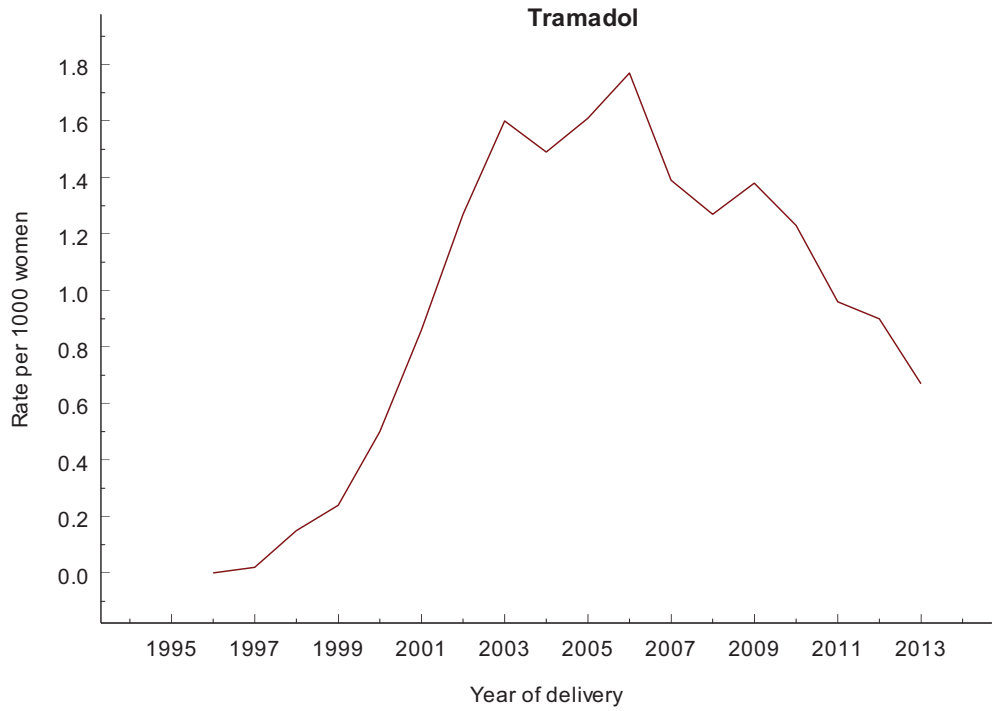

Fig. 1. Rate of women who reported the use of tramadol in early pregnancy per 1000 women among those who gave birth in 1997–2013.

Table 3
Malformation diagnoses among 96 infants born of women who reported the use of tramadol in early pregnancy, nine of which were born to women who reported unwanted childlessness (subfertility).

Diagnosis	Number	Note
Major malformations		
Spina bifida	1	
Occipital encephalocele	1	
Microphthalmia	1	
Inner ear malformations	1	
Isolated cardiovascular defect	22	
Diaphragmatic hernia + truncus communis	1	1 subfertile
Esophageal atresia + ECD	1	
VSD + undescended testicle	1	
VSD + knee, foot and hip deformity	1	
Cleft lip or cleft palate	2	
Median cleft palate	1	
Pyloric stenosis	2	
Hypospadias	5	
Renal dysplasia	1	
Hydronephrosis	2	1 subfertile
Polydactyly	4	
Pes equinovarus	9	2 subfertile
Unspecified foot deformity	1	
Craniostenosis	1	
Fibular longitudinal reduction deformity	1	
Diaphragmatic hernia	1	
Neurofibromatosis	1	1 subfertile
Down syndrome	2	
Minor or uncertain malformations		
Iris coloboma	1	
Minor ear anomalies including preauricular tag	7	1 subfertile
Patent ductus at preterm birth	3	
Tongue tie	3	1 subfertile
Tongue tie + hip (sub) luxation	1	
Tracheomalacia	1	
Undescended testicle	4	1 subfertile
Urinary reflux	1	
Isolated unstable hip, hip (sub) luxation	8	
Nevus	3	1 subfertile
Unspecified malformation	1	

ECD: endocardial cushion defect, VSD: ventricular septum defect.

Table 4
Some characteristics of women reporting the use of tramadol in early pregnancy compared with other women who gave birth, 1997–2011.

Variable	Number with tramadol	Total number	OR	95% CI
Maternal age				
<20	20	28887	**0.54**	**0.34–0.85**
20–24	245	228357	1.00	0.85–1.17
25–29	500	515338	1.00	Reference
30–34	541	577150	0.92	0.81–1.04
35–39	342	276916	1.06	0.91–1.23
40–44	98	53429	**1.32**	**1.03–1.68**
≥45	5	1969	1.47	0.68–3.57
Parity				
1	671	747829	1.00	Reference
2	487	613477	**0.89**	**0.79–1.00**
3	340	225479	**1.40**	**1.30–1.73**
≥4	253	98061	**2.03**	**1.71–2.42**
Smoking				
Unknown	25	91406	–	–
None	11999	1443964	1.00	Reference
<10 cigs/day	342	101 464	**3.92**	**3.50–4.38**
≥10 cigs/day	185	38158	**5.36**	**4.13–6.17**
BMI				
Unknown	97	191748	–	–
<18.5	33	36688	0.97	0.68–1.37
18.5–24.9	794	913164	1.00	Reference
25–29.9	475	371795	**1.26**	**1.12–1.41**
30–34.9	235	120484	**1.67**	**1.45–1.93**
≥35	117	48967	**1.77**	**1.47–2.15**
Years of unwanted childlessness				
0	1500	1547029	1.00	Reference
1	50	43031	1.19	0.90–1.57
2	45	38166	1.26	0.93–1.69
≥3	76	49604	**1.61**	**1.27–2.03**
Total	1751	1682846	–	–

Odds ratio (OR) with 95% confidence interval (95% CI). OR for each variable is adjutewd fro year of delivery and the other tabulated variables. Bold text marks statistical significance.

Table 5
Some drug categories used together with tramadol.

Drug	Number with Tramadol	Total number	OR/RR	95% CI
Drugs for GERD	78	14830	**4.28**	**3.47–5.28**
Insulin	11	5822	1.53	0.76–2.34#
Folic acid	106	121007	**0.77**	**0.63–0.94**
Drugs for hypertension	30	5734	**3.93**	**2.66–5.61#**
Oral contraceptives	16	4117	**3.15**	**1.80–5.11#**
Gestagens	2	8227	–	–
Ovarian stimulation	1	2624	–	–
Corticosteroids	26	5723	**4.64**	**3.26–6.60**
Thyroid drugs	34	30113	0.99	0.70–1.39
Antibiotics	77	36282	**2.06**	**1.65–2.58**
NSAIDs	302	23786	**11.6**	**10.5–12.8**
Mild analgesics	621	103477	**7.54**	**6.94–8.20**
Drugs for migraine	31	3950	**7.19**	**4.89–10.2#**
Anticonvulsants	46	4718	**6.46**	**4.73–8.62#**
Neuroleptics	5	4046	0.90	0.29–2.10#
Sedatives/hypnotics	206	7607	**15.7**	**14.0–17.5#**
Antidepressants	220	27431	**5.30**	**4.68–6.02**
Antiasthmatics	104	46543	**1.99**	**1.64–2.92**
Antihistamines	136	90832	**1.48**	**1.24–1.86**

GERD: gastroesophageal reflux diagnosis.
NSAID: non-steroid antiinflammatory drug.
Odds ratios (OR) or risk ratios (RR, marked #) with 95% confidence interval (95% CI) for use of other drugs among tramadol users ($n = 1579$) and use of other drugs among non-users ($n = 1\,456\,722$). Bold text marks statistical significance.

reported the use of anticonvulsants or hypertension drugs hardly changed the risk estimates and none of the cases with a cardiac defect or pes equinovarus had reported any of these drugs.

For comparisons, infants exposed to opioids other than tramadol were investigated. Codeine use showed a significant risk estimate for any and for relatively severe congenital malformation. There was no significant risk increase after dextropropoxyphene use but the estimate for pes equinovarus was non-significantly high. No risk increase was seen after other natural opiates than codeine. After synthetic opioids (excluding dextropropoxyphene and tramadol) a formally significant increase in any cardiovascular defect was seen, based on seven cases. No case of pes equinovarus was seen after such exposures (Table 6).

4. Discussion

As far as we know this is the first relatively large study of possible teratogenic effects of tramadol used during early pregnancy. It was based on Swedish health registers and the information on drug use was obtained by interviews in early pregnancy. This basically excludes recall or interviewer bias. The ascertainment of congenital malformations was made from three different sources and was probably also unbiased and close to complete. Among the 26 cardiovascular defects, all but three were recorded in the Medical Birth Register, 10 were reported in the Birth Defect Register, and 9 in the Hospital Discharge Register.

The study only referred to infants born. Fetuses aborted because of a detected congenital malformation were not possible to identify due to Swedish legal restrictions. This made it impossible to ascertain drug exposures. It would be impossible to detect an association with fetuses with a malformation (like anencephaly), which is nearly always aborted. If such fetuses were sometimes, but not always, aborted (*e.g.* spina bifida) it would be possible to reveal an association even though the power of the study would be reduced.

A weakness of the study methodology is that information on dosage and pregnancy week when the drug was taken were recorded but this information is often vague and of little use. Some drug use may consists of very few tablets and perhaps outside the organogenetic period—if so it will bias the risk estimate towards unity. One specific complication is the use of strong analgesics in connection with egg sampling for *in vitro* fertilization. Such exposure may occur before embryo transfer or during the very first period of intrauterine development, before organogenesis starts. We did see an association with the number of years with unwanted childlessness (as a proxy for *in vitro* fertilization) and the use of tramadol. If the women who had reported a period of unwanted childlessness (about 10%) were removed from the analysis it resulted in a slight increase in the risk estimate for a congenital malformation which would agree with this idea.

As shown in Fig. 1 the use of tramadol in pregnant women increased and reached its maximum in 2006. The decline since then is probably a result of an increased awareness of the drug's

Table 6
Risk estimates for specific malformations after maternal use of opiates or other opioids than tramadol in early pregnancy.

Malformation and drug	No. with opioid	OR/RR	95% CI
Codeine with paracetamol or ASA($n = 2655$)			
Any malformation	128	**1.42**	**1.19-1.69**
Relatively severe malformation	93	**1.42**	**1.15-1.76**
Any cardiovascular defect	31	1.38	0.97-1.96
Isolated septum defect	16	1.31	0.80-2.14
Pes equinovarus	4	1.24	0.34-3.18#
Other natural opiates than codeine ($n = 556$)[a]			
Any malformation	24	1.20	0.80–1.81
Relatively severe malforomations	19	1.17	0.71–1.93
Any cardiovascular defect	4	0.86	0.23–2.19#
Dextropropoxyphene, alone or with paracetamol or ASA ($n = 3265$)			
Any malformation	163	1.07	0.91–1.26
Relatively severe malformation	109	1.06	0.87–1.28
Any cardiovascular defect	31	0.97	0.68–1.32
Isolated septum defect	16	1.01	0.62–1.66
Pes equinovarus	8	1.68	0.72–3.30#
Other synthetic opioids except tramadol and dextropropoxyphene ($n = 315$)[b]			
Any malformation	16	1.25	0.75–2.08
Relatively severe malformation	14	1.30	0.71–2.38
Any cardiovascular defect	7	**2.94**	1.18–6.06#
Isolated septum defect	5	1.59	0.52–3.72#
Pes equinovarus	0	–	–

Odds ratio (OR) or risk ratio (RR, marked #) with 95% confidence interval (95% CI) after adjustment for year of delivery, maternal age, parity, smoking, and BMI. ASA: acetyl salicylic acid.

[a] morphine ($n = 494$), oxycodone ($n = 69$), hydromorphone ($n = 23$).

[b] ketobemidone ($n = 267$), fentanyl ($n = 11$), pethidine ($n = 27$), pentazocine ($n = 5$), unspecified ($n = 5$).

abuse potentials. Tramadol may have been abused by some pregnant women, but usually drug abuse is incompletely recorded in the interview by the midwife. However, there was a strong association between use of tramadol and maternal smoking which could be a weak indicator of abuse. The effects of tramadol on cardiovascular defects or pes equinovarus were slightly stronger for non-smokers than for smokers but the difference was far from statistically significant.

The women using tramadol also used many other drugs in excess. Some of them have teratogenic effects like anticonvulsants and drugs used for hypertension. Exclusion of women using also these drugs did not change the risk estimates notably. The material was not large enough to permit more specific analyses of tramadol combined with other drug categories. Such an analysis could otherwise have indicated areas of use, specifically linked to a teratogenic effect, and in this way identify possible confounding by indication.

Some information on confounding by indication can be obtained by studies of other strong analgesics. In the present study there were little signs of teratogenicity of dextropropoxyphene but a significant effect of codeine. The latter finding contrasts to a Norwegian study [7] based on prospectively ascertained exposure information. A study from the American National Birth Defects Prevention Study [13] found an association between opioid use and a number of specific malformations but the study was retrospective with a possibility of recall bias and also had a high rate of non-responders and has therefore little informative value.

Natural opiates except codeine seemed to have no teratogenic effect but in the present study there were slight signs of a teratogenic effect of synthetic opioids (even in the absence of tramadol). It is, however, noteworthy that no case of pes equinovarus was seen with other opioids so that risk seems to be typical of tramadol.

This leads us to a discussion that perhaps tramadol should not be compared with other opioids, neither natural nor synthetic. The analgesic effects induced by tramadol are mediated through two different mechanisms: through a modest affinity for μ-opioid receptors (10-fold less potent than codeine and 6000-fold weaker than morphine), and through a reuptake inhibiting effect on noradrenaline (NA) and serotonin (5-HT) with about equal potency [14]. Tramadol is a racemic mixture of two enantiomers and both contribute to the analgesic activity: (+)-tramadol and the metabolite (+)-*O*-desmethyl-tramadol are agonists of the μ-opioid receptor. The 5-HT reuptake inhibition is mediated by (+)-tramadol, and (−)-tramadol inhibits NA reuptake [15]. Tramadol is metabolized primarily by *O*- and *N*-demethylation. Formation of the pharmacologically active metabolite *O*-desmethyltramadol is catalyzed by the highly polymorphic enzyme cytochrome P450 (CYP) 2D6 [16] whereas catalysis to the metabolite *N*-desmethyltramadol is mediated by CYP2B6 and CYP3A4 [17]. *O*- and *N*-demethylation of tramadol as well as renal elimination are stereo selective and the wide variability in the pharmacokinetic properties of tramadol can partly be ascribed to CYP polymorphism. Based on the pharmacological NA and 5-HT reuptake features of tramadol it should perhaps be compared with antidepressant drugs, foremost with tricyclic antidepressants (TCA) and serotonin/noradrenalin inhibitors (SNRI). Worth noting is also that the tramadol molecular structure is similar to that of venlafaxine [18].

Even if tramadol and some antidepressants are structurally similar the major indications differ: pain and depression. Nevertheless, both TCAs and SNRIs have the indication as pain reducer and are frequently used as such. Worth noting are also the characteristic similarities between the women taking antidepressants [19] and tramadol: Both groups had high BMI and smoked and they used an excess of other drugs during early pregnancy in a different pattern than other women (*e.g.*, drugs for GERD, drugs for hypertension, anti-asthmatics, NSAID, and antihistamines). The most important use of co-medication which the women have in common refers to other psychoactive drugs with a very high usage of sedatives and hypnotics but also neuroleptics, drugs for migraine, and anticonvulsants. This may indicate co-morbidities which might be similar in women taking tramadol and women taking an antidepressant drug.

5. Conclusion

The results of this study need confirmation from other studies but suggest a weak teratogenic effect of tramadol, specifically with respect to cardiovascular defects and pes equinovarus. To conclude, until further information is available, avoidance of tramadol use during early pregnancy may be recommended. If exposure has occurred, the absolute risk is small and the malformations observed are not very serious why there is little reason to discuss an interruption of pregnancy because of such exposure.

Conflicts of interest

None of the authors has a conflict of interest.

Author contributions

The study was planned by the authors jointly, BK collected and analyzed the data and wrote the first draft. MR commented upon and supplemented the draft. Both authors have read and accepted the final manuscript.

Ethics

The study was performed within the responsibilities of the National Board of Health and Welfare and therefore no ethical approval from outside ethical committees was needed.

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