

Exposure to topical chloramphenicol during pregnancy and the risk of congenital malformations: a Danish nationwide cohort study

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ABSTRACT.

Purpose: To investigate whether exposure to topical chloramphenicol in the first trimester of pregnancy is associated with congenital malformations.

Methods: The authors conducted a nationwide cohort study including all women giving live birth between 1997 and 2011 in Denmark. All women redeeming at least one prescription of chloramphenicol eye drops or eye ointment during the first 84 days of pregnancy were identified. Logistic regression was used to estimate the odds ratios of malformations among exposed women compared to non-exposed women.

Results: 966 372 births between 1997 and 2011 were included. A total of 6024 women were exposed to topical chloramphenicol in the first trimester. The rate of congenital malformations was 3.50% among offspring of exposed mothers and 3.49% among unexposed. Exposure to topical chloramphenicol in the first trimester was not associated with major congenital malformations (adjusted odds ratio = 1.06, 95% CI 0.91–1.22) or specific major malformations. The number of redeemed prescriptions decreased significantly during pregnancy as compared to before and after pregnancy ($p < 0.0001$).

Conclusion: In this study, we found no association between dispensing of chloramphenicol eye drops or eye ointment in the first trimester of pregnancy and major congenital malformations. This is in accordance with a previous study analysing the risk of systemic chloramphenicol.

Key words: congenital malformations – pregnancy – topical chloramphenicol

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Introduction

Topical chloramphenicol is widely used against infectious eye disease (Walker & Hinchliffe 2010), but limited evidence on its safety during pregnancy exists. Few antibiotic agents have been proved to be teratogenic. However, there is evidence

that pregnant women and physicians overestimate the risks associated with drug use during pregnancy (Sanz et al. 2001; Nordeng et al. 2010).

Chloramphenicol is known to cause 'grey baby syndrome' in neonates (Mulhall et al. 1983), and fatal aplastic

anaemia following long-term use of chloramphenicol eye drops has been reported (Rosenthal & Blackman 1965; Carpenter 1975; Fraunfelder et al. 1982).

This study is the first to investigate potential foetal risks associated with topical chloramphenicol during pregnancy. We performed a population-based cohort study including all births in Denmark between 1997 and 2011, estimating the association between exposure to chloramphenicol eye drops or eye ointment in the first trimester and congenital malformations.

Materials and Methods

We identified 977 706 births in the study period between 1997 and 2011. 7215 records were excluded due to coding errors and 4119 due to stillbirths. The final cohort consisted of 966 372 births. Information on births was collected from the Danish Medical Birth Registry (Knudsen & Olsen 1998), and information on drug redemption was gathered from the Danish National Prescription Registry (Kildemoes et al. 2011). Information on congenital malformations was obtained from the Danish National Hospital Register (Andersen et al. 1999). All records were linked using a unique personal identification number given to all Danish residents at birth or upon immigration (Pedersen et al. 2006). Children given a primary or secondary diagnosis of a major congenital malformation within the first year after

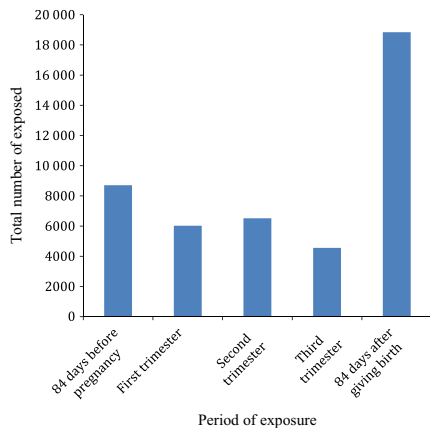


Fig. 1. Number of women exposed to topical chloramphenicol before, during and after pregnancy.

birth were classified as having a major congenital malformation, according to the European Surveillance of Congenital Anomalies (EUROCAT) classification system guide 1.3 (European Surveillance of Congenital Anomalies 2005).

Exposure was defined as redemption of at least one prescription of chloramphenicol eye drops or eye ointment [Anatomical Therapeutic Chemical Classification (ATC) S01AA01] within the first 84 days of pregnancy.

Statistics

Logistic regression was used to estimate the odds ratio (OR) of malformations

among women redeeming a prescription of chloramphenicol in the first trimester of pregnancy compared to women not redeeming a prescription in the first trimester. The models were adjusted for maternal age, year of giving birth, number of previous births, educational length, income, smoking during pregnancy and marital status. A two-sided value of $p < 0.05$ was considered statistically significant. Odds ratios are presented with 95% confidence intervals.

Results

We identified 6024 women redeeming a prescription of chloramphenicol during the first trimester of pregnancy. Exposed women were more likely to be older ($p < 0.0001$), have longer education ($p < 0.0001$), have higher household income ($p < 0.0001$), to be married ($p < 0.0001$) and having experienced multiple pregnancies compared to unexposed ($p = 0.002$). There was no observed difference in smoking habits ($p = 0.52$) or prepregnancy Body Mass Index ($p = 0.87$). The rate of exposed women was lower during pregnancy as compared to 3 months before and after pregnancy ($p < 0.0001$) (Fig. 1). Among chloramphenicol-exposed pregnancies, 211 (3.50%) had a diagnosis of a major congenital malformation compared to

33476 (3.49%) among unexposed. There was no association between exposure to chloramphenicol in the first trimester and major congenital malformation in general (OR = 1.06; CI 95% 0.91–1.22) or any subgroupings (Table 1) compared to unexposed.

Discussion

In the present cohort study of nearly one million pregnancies over a 16-year period, we observed no increased risk of major congenital malformations among offspring exposed to topical chloramphenicol in the first trimester of pregnancy, compared to unexposed. These findings are comparable to a previous small case-control study that found no increased teratogenic risk associated with oral chloramphenicol use during pregnancy (Czeizel et al. 2000). The occurrence of congenital malformations as a result of drug use requires absorption into the systemic circulation. Even though topical chloramphenicol at the most only results in a very low systemic absorption, (Trope et al. 1979), aplastic anaemia after topical chloramphenicol treatment has been described in several case reports (Rayner & Buckley 1996). A major limitation of this study is that we do not have information on the duration and dosage of use, or if the women used the drops at all,

Table 1. Odds ratios for major congenital malformations in the offspring of women exposed to chloramphenicol during the first trimester.

Type of major malformation	Number of offspring diagnosed with a major malformation		Odds ratio (CI 95%)	
	Exposed <i>n</i> = 6024	Unexposed <i>n</i> = 960348	Unadjusted	Adjusted
Congenital malformations of the nervous system	9 (0.15%)	1474 (0.15%)	0.97 (0.51–1.88)	1.16 (0.60–2.24)
Neural tube defects	1 (0.02%)	393 (0.04%)	0.41 (0.06–2.89)	0.46 (0.07–3.30)
Congenital malformations of the eye	6 (0.10%)	1163 (0.12%)	0.82 (0.37–1.84)	0.63 (0.24–1.68)
Congenital malformations of the ear, face and neck	0 (0.0%)	294 (0.03%)	*	*
Congenital malformations of the heart	67 (1.11%)	9109 (0.95%)	1.18 (0.92–1.50)	1.24 (0.96–1.61)
Oro-facial clefts	10 (0.17%)	1821 (0.19%)	0.88 (0.47–1.63)	0.88 (0.46–1.69)
Congenital malformations of the digestive system	13 (0.22%)	1973 (0.21%)	1.05 (0.61–1.82)	1.07 (0.59–1.93)
Congenital malformations of the internal urinary system	11 (0.18%)	2921 (0.30%)	0.60 (0.33–1.09)	0.64 (0.34–1.18)
Congenital malformations of the external genital organs	18 (0.30%)	2844 (0.30%)	1.01 (0.63–1.61)	1.10 (0.69–1.78)
Congenital malformations of the limbs	55 (0.91%)	9551 (0.99%)	0.92 (0.70–1.20)	1.00 (0.76–1.32)
Congenital malformations of the musculoskeletal system	12 (0.20%)	1540 (0.16%)	1.24 (0.70–2.20)	1.39 (0.77–2.52)
Chromosomal abnormalities	16 (0.27%)	1375 (0.14%)	1.86 (1.13–3.04)	1.63 (0.94–2.82)
Teratogenic syndromes with malformations	0 (0.0%)	86 (0.01%)	*	*
Genetic syndromes and microdeletions	7 (0.12%)	802 (0.08%)	1.39 (0.66–2.93)	1.61 (0.76–3.39)
Other malformations	9 (0.15%)	1425 (0.15%)	1.01 (0.52–1.94)	1.05 (0.52–2.10)
Congenital malformations of the respiratory system	6 (0.10%)	1229 (0.13%)	0.78 (0.35–1.74)	0.95 (0.43–2.12)
Abdominal wall defects	2 (0.03%)	290 (0.03%)	1.10 (0.27–4.42)	0.78 (0.11–5.56)
All major congenital malformations	211 (3.50%)	33476 (3.49%)	1.01 (0.88–1.15)	1.06 (0.91–1.22)

* Not relevant.
CI 95%, 95% confidence interval.

increasing the risk of misclassifying exposure (Sawicki et al. 2011; Lupattelli et al. 2014). It is important to take this into account when interpreting the results of this study. There is also the risk of overseeing an increased risk of malformations with a very low prevalence, for example of the splanchno-pleura and neural tube, previously found in chloramphenicol-exposed chick embryos (Billett et al. 1965). In rats, excessive chloramphenicol exposure in early pregnancy is associated with increased rates of omphalocele and umbilical hernia (Fritz & Hess 1971).

We observed a 30% decrease in chloramphenicol exposure from pre-conception to first trimester of pregnancy (Fig. 1). A possible explanation could be reluctance from physicians in prescribing chloramphenicol during pregnancy, or pregnant women avoiding to redeem prescriptions. If this is true, studies analysing the teratogenic potential of chloramphenicol are warranted. To validate our findings, it would be obvious to analyse the risk of systemic chloramphenicol, but data are not available, as systemic chloramphenicol has not been used during pregnancy in Denmark within the study period. The use of population-based registries minimizes the risk of selection bias and ensures a high registration coverage of prescriptions (Sørensen et al. 1996). The Medical Birth Registry keeps records of more than 99% of all births in Denmark (Kristensen et al. 1996), and the Danish National Hospital Registry holds more than 99% of all discharge records from all Danish hospitals (The Danish National Board of Health 2004). Recall bias was eliminated as the use of prescription data did not rely on self-reported use, and all data were registered prospectively.

Conclusion

In the present study, we found no association between dispensing of chloramphenicol eye drops or eye

ointment in the first trimester of pregnancy and major congenital malformations. This is in accordance with a previous study analysing the risk of systemic chloramphenicol.

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