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Exposure to antazoline-naphazoline eye drops during pregnancy and the risk of congenital malformations: a Danish nationwide cohort study

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ABSTRACT.

Purpose: **To investigate whether exposure to antazoline-naphazoline eye drops in the first trimester of pregnancy was associated with an increased risk of malformations in humans.**

Methods: **All women giving live birth between 1997 and 2011 in Denmark were included in this nationwide cohort study. All women redeeming at least one prescription of antazoline-naphazoline eye drops during the first 84 days of pregnancy were identified. Logistic regression was used to estimate the odds ratios of malformations among exposed offspring compared to non-exposed offspring.**

Results: **We identified 977 706 births between 1997 and 2011. A total of 3061 women (0.32%) were exposed to antazoline-naphazoline eye drops in the first trimester of pregnancy. The rate of congenital malformations was 3.0% (n = 93) in exposed offspring and 3.5% (n = 33 594) in unexposed offspring. First-trimester exposure to antazoline-naphazoline was not associated with major congenital malformations overall (odds ratio: 0.88, 95% confidence interval: 0.71–1.09) or with any specific major malformation. The number of redeemed prescriptions was unchanged during all trimesters of pregnancy as compared to before and after pregnancy ($p < 0.05$).**

Conclusion: **Exposure to antazoline-naphazoline eye drops in the first trimester of pregnancy appears not to be associated with increased teratogenic risk.**

Key words: antazoline-naphazoline – eye drops – pregnancy – safety – topical

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Introduction

Ocular allergy affects up to 40% of the population in developed countries (La Rosa et al. 2013), and antihistamines along with sympathomimetics are among the most frequently used medications in pregnancy (Werler et al. 2005; Thorpe et al. 2013). Antazoline-naphazoline eye drops comprise a first-generation antihistamine (antazoline) in combination with a sympathomimetic (naphazoline). Current evidence indicates that oral antihistamines pose little risk to exposed foetuses (Pedersen et al. 2006a,b; Gilboa et al. 2009; Li et al. 2013). However, concerns about the fetal safety of different antihistaminic agents centre around their teratogenic potential (Kar et al. 2012). Exposure to oral sympathomimetics in early pregnancy has been associated with congenital malformations such as gastroschisis, small intestinal atresia and hemifacial microsomia (Werler et al. 2002, 2003, 2004). A recent case–control study also found increased risk of pyloric stenosis and tracheoesophageal fistula following first-trimester exposure to intranasal sympathomimetics (Yau et al. 2013). The systemic concentration of antazoline-naphazoline is probably low, as it is applied topically. Nevertheless, adverse systemic effects such as increase in blood pressure and cardiac arrhythmias are known complications to high-dose sympathomimetic eye drops (Hakim et al. 1990; Fraunfelder et al. 2002; Stavert et al. 2015). Little is known about the potential negative effects caused by anti-allergy eye drop exposure during pregnancy, and the lack of fetal safety data may create unnecessary worry in expecting mothers and their physicians (Nordeng et al. 2010). The present study is the first to explore potential fetal risks associated with first-trimester exposure to ocular antihistamines in combination with sympathomimetics. We included all

pregnant women giving live birth in Denmark between 1997 and 2011 and investigated the association between first-trimester exposure to antazoline-naphazoline and the risk of congenital malformations.

Materials and Methods

During the 1997–2011 study period, we identified in total 977 706 births. We excluded 7215 records either due to coding errors in information on gestational length (3096) or because they were stillbirths (4119). The information on births was obtained from the Danish Medical Birth Registry (Knudsen & Olsen 1998). Records on prescription drug use were obtained from the Danish National Prescription Registry (Kildemoes et al. 2011), and 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 assigned to all Danish residents at birth or upon immigration (Pedersen et al. 2006a,b).

The Danish Medical Birth Registry contains individual-level data on the mother, assumed father and child. The registry includes data on age, previous births and abortions, as well as birth weight and length, sex and gestational age of the offspring. The time of conception is based on ultrasonograms or information on the date of the last menstrual period. Since 1978, the registry has included more than 99.5% of all births in Denmark (Knudsen & Olsen 1998).

Children born with major congenital malformations were identified through the Danish National Hospital Register. Children are given a primary or secondary diagnosis of a major congenital malformation within the first year after birth were classified as having a major congenital malformation. All major congenital malformations and subgroupings were classified according to the European Surveillance of Congenital Anomalies classification system guide 1.3 (European Surveillance of Congenital Anomalies 2005). The register contains information on all hospitalizations since 1977, including admittance data and discharge diagnosis. All diagnoses were registered according to the International Classification of Diseases 10th Danish revision. The Danish National Hospital Register contains more than 99% of discharge records from all Danish hospitals (The Danish National Board of Health. 2004).

Information on prescription medication use was obtained from the Danish National Prescription Registry (Kildemoes et al. 2011). Exposure was defined as the redemption of at least one prescription of antazoline-naphazoline eye drops (Anatomical Therapeutic Chemical Classification S01GA51) within the first 84 days of pregnancy. The register contains data on all prescribed drugs dispensed from pharmacies in Denmark since 1994. Rate of coverage has been estimated to 97.5% (Sørensen et al. 1996).

However, the register has no information on the indication of treatment or individual sale of over-the-counter drugs. Length of education was gathered from the Populations Education Register, which contains information on the standardized length of education, highest level of education completed and detailed individual education history (Jensen & Rasmussen 2011). Information on income was acquired from the Income Statistics Register, which among others contains information on taxes, entrepreneurial income, salary, public transfer payments and pay-outs (Baadsgaard & Quitzau 2011).

Statistics

All data management and analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Logistic regression was used to estimate the odds ratio of malformations among women redeeming a prescription of antazoline-naphazoline eye drops in the first trimester of pregnancy compared to those who did not. The models were adjusted for maternal age (<20, 20–24, 25–29, 30–34, ≥35 years), year of giving birth (1997–2000, 2001–2005, 2006–2011), number of previous births (0, 1, 2, ≥3), length of education (0–143, 144–155, 156–179, >180 months), income (in quartiles: lowest, low, medium, high) and smoking during pregnancy (yes/no). There was <1% missing data on maternal age, previous births and income. Data on education level were missing for 3.4% of the records, as was 3.1% of data on smoking and 3.3% of education data. For all analyses, a two-sided p-value <0.05 was considered statistically significant, and all odds ratios were presented with 95% confidence intervals (CI). The use of antazoline-naphazoline eye drops before, during and after birth is reported as redeemed prescriptions per week per 10 000 pregnant women.

Ethics

The Danish Data Protection Agency approved the study (No. 2008-41-2517). All data were linked using computers held by Statistics Denmark and were made available with encrypted personal information. This ensured that no individual could be identified. In Denmark, the Act on Processing of Personal Data does not require ethical approval or written informed consent for anonymized retrospective register studies. We report our findings according to strengthening the reporting of observational studies in epidemiology guidelines (Von Elm et al. 2014).

Results

We included 966 372 live births in the 1997–2011 study period. A total of 3061 women (0.32%) were exposed to antazoline-naphazoline eye drops in the first trimester of pregnancy. The rate of redeemed prescriptions during all trimesters of pregnancy was unchanged compared to before and after pregnancy (Fig. 1).

Maternal characteristics

Women who received antazoline-naphazoline eye drops were more likely to be older ($p < 0.001$), have longer length of education ($p < 0.001$), higher household income ($p < 0.001$) and having given birth previously ($p < 0.001$). They were less likely to smoke during pregnancy ($p < 0.001$; Table 1).

Pregnancy outcome

We identified 33 687 offspring (3.49%) with a diagnosis of congenital malformation. The rate of congenital malformations was 3.0% ($n = 93$) among offspring exposed to antazoline-naphazoline eye drops compared to 3.5% ($n = 33\,594$) among unexposed offspring (Table 2). First-trimester exposure to antazoline-naphazoline eye drops was not associated with major

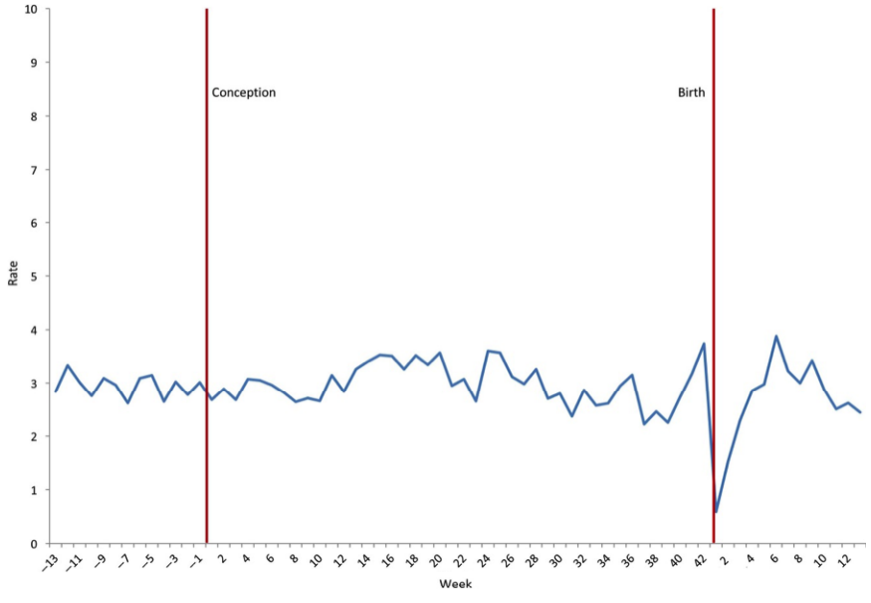

Fig 1. Eye drop exposure. The number of antazoline-naphazoline prescriptions redeemed per week per 10 000 pregnant women, before, during and after pregnancy.

Table 1. Basic characteristics.

	Use of antazoline-naphazoline during first trimester of pregnancy No. (%) n = 3061	No use of antazoline-naphazoline during first trimester of pregnancy No. (%) n = 963 311	p-value (unpaired t-test)
Age (years)			
<20	18 (0.6)	14 310 (1.5)	<0.001
20–24	222 (7.3)	111 161 (11.5)	
25–29	1076 (35.2)	323 505 (33.6)	
30–34	1225 (40.0)	345 448 (35.9)	
≥35	520 (17.0)	168 887 (17.5)	
Education (years)			
<12	507 (18.9)	223 645 (24.0)	<0.001
12–13	462 (15.3)	148 206 (15.9)	
13–15	950 (31.4)	270 370 (29.0)	
>15	1042 (34.5)	288 990 (31.0)	
Income (quartiles)			
Lowest quartile	597 (19.5)	240 912 (25.0)	<0.001
Low quartile	815 (26.6)	240 693 (25.0)	
Medium quartile	826 (27.0)	240 682 (25.0)	
High quartile	823 (26.9)	240 685 (25.0)	
Parity			
1	1317 (43.2)	421 195 (44.0)	<0.001
2	1117 (36.6)	352 909 (36.9)	
3	452 (14.8)	133 514 (14.0)	
≥4	163 (5.4)	49 299 (5.2)	
Smoking during pregnancy	313 (10.6)	169 509 (18.2)	<0.001

congenital malformations overall, with an adjusted odds ratio of 0.88 (95% CI: 0.71–1.09) compared to unexposed pregnancies. Furthermore, we found no association between exposure to antazoline-naphazoline and any specific major congenital malformation subgrouping (Table 2). We specifically investigated a possible association between antazoline-naphazoline and specific major malformations previously associated with oral sympathomimetic use in early pregnancy. There was no association between exposure to antazoline-naphazoline and gastroschisis [adjusted odds ratio = 1.10 (95% CI: 0.16–7.87)], small intestinal atresia or hemifacial microsomia (Table 3).

Discussion

Albeit a study population of nearly one million pregnancies, we did not observe increased risk of major congenital malformations among offspring exposed to antazoline-naphazoline in the first trimester, compared to that of non-exposed offspring. We tested specifically for potential associations between antazoline-naphazoline exposure and gastroschisis, small intestinal atresia and hemifacial microsomia, as these conditions have been associated with oral sympathomimetic use in early pregnancy (Werler et al. 2002, 2003, 2004). Our findings do not replicate these observations. The overall prevalence of congenital malformations was 3.5%, similar to that found in other studies (Egbe et al. 2015). Our findings are comparable to the majority of previous case–control and epidemiologic studies that detected no increased risk following first-trimester exposure to oral antihistamines and sympathomimetics (Einarson et al. 1997; Källén & Mottet 2003; Källén & Olausson 2006). Surprisingly, we found that the number of redeemed prescriptions of antazoline-naphazoline during all trimesters of pregnancy was unchanged compared to the period before and after pregnancy. This finding contrasts sharply with a substantial decrease in chloramphenicol eye drop exposure during pregnancy in the same study population (Thomseth et al. 2015). A likely explanation of this finding would be that despite lack of fetal safety data, over-the-counter drugs are generally viewed as safe for use with respect to pregnancy complications.

The strengths of this study are the large sample size, that is 3061 women exposed to antazoline-naphazoline, and its nationwide coverage, which included all women giving live birth in Denmark during the study period. The use of population-based registries minimized the risk of selection bias and ensured high registration coverage of prescriptions. Danish pharmacies are obliged to register all redeemed prescriptions, ensuring that the Danish National Prescription Registry covered all redemptions of antazoline-naphazoline prescriptions within the study period (Sørensen et al. 1996). A limitation of the study is the likely underestimation of antihistamine and sympathomimetic eye drop exposure during pregnancy, as these drugs are

Table 2. Exposure to antazoline-naphazoline in the first trimester of pregnancy and the risk of congenital malformations

Type of major malformation	Number of offspring diagnosed with a major malformation		Odds ratio (95% confidence interval)	
	Exposed n = 3061 (%)	Unexposed n = 963 311 (%)	Unadjusted	Adjusted
All major congenital malformations	93 (3.0)	33 594 (3.5)	0.87 (0.71–1.07)	0.88 (0.71–1.09)
Congenital malformations of the nervous system	2 (0.1)	1481 (0.2)	0.43 (0.11–1.70)	0.47 (0.12–1.90)
Neural tube defects	0 (0.0)	394 (0.0)	–	–
Congenital malformations of the eye	1 (0.1)	1168 (0.1)	0.27 (0.04–1.91)	0.30 (0.04–2.10)
Congenital malformations of the ear, face and neck	1 (0.0)	293 (0.0)	1.08 (0.15–7.65)	1.16 (0.16–8.27)
Congenital malformations of the heart	29 (0.9)	9147 (0.9)	1.00 (0.69–1.44)	1.04 (0.71–1.53)
Orofacial clefts	1 (0.1)	1830 (0.2)	0.17 (0.02–1.22)	0.18 (0.03–1.28)
Congenital malformations of the digestive system	4 (0.2)	1982 (0.2)	0.64 (0.23–1.70)	0.52 (0.17–1.62)
Congenital malformations of the internal urinary system	9 (0.3)	2923 (0.3)	0.97 (0.50–1.87)	0.95 (0.47–1.90)
Congenital malformations of the external genital organs	11 (0.4)	2851 (0.3)	1.22 (0.67–2.20)	1.34 (0.74–2.43)
Congenital malformations of the limbs	22 (0.7)	9584 (1.0)	0.72 (0.47–1.10)	0.69 (0.45–1.07)
Congenital malformations of the musculoskeletal system	4 (0.3)	1548 (0.2)	0.81 (0.31–2.17)	0.67 (0.22–2.08)
Chromosomal abnormalities	9 (0.3)	1382 (0.1)	2.06 (1.07–3.96)	1.88 (0.94–3.77)
Teratogenic syndromes with malformations	0 (0.0)	86 (0.0)	–	–
Genetic syndromes and microdeletions	3 (0.1)	806 (0.1)	1.17 (0.38–3.64)	1.33 (0.43–4.15)
Other malformations	5 (0.2)	1429 (0.2)	1.10 (0.46–2.65)	1.21 (0.50–2.92)
Congenital malformations of the respiratory system	2 (0.2)	1233 (0.1)	0.51 (0.13–2.04)	0.62 (0.15–2.48)
Abdominal wall defects	0 (0.0)	292 (0.0)	–	–

Table 3. Exposure to antazoline-naphazoline eye drops in the first trimester of pregnancy and the risk of selected congenital malformations previously associated with oral sympathomimetic use.

Type of major malformation	Number of offsprings diagnosed with a major malformation		Odds ratio (95% confidence interval)	
	Exposed n = 3061 (%)	Unexposed n = 963 311 (%)	Unadjusted	Adjusted
Congenital absence, atresia and stenosis of small intestine	1 (0.0)	323 (0.0)	0.98 (0.14–6.94)	1.10 (0.16–7.87)
Gastroschisis	0 (0.0)	168 (0.0)	–	–
Congenital malformation syndromes predominantly affecting facial appearance including Goldenhar syndrome	0 (0.0)	295 (0.0)	–	–

sold over-the-counter in Denmark. This could have led to exposed women being misclassified as unexposed. During the study period, 38.6% of antazoline-naphazoline eye drops were sold over-the-counter (The Register of Medicinal Product Statistics n.d.). We do not, however, believe that this confounded our risk estimates of major congenital malformations.

The risk estimates of this study have been adjusted for selected basic demographic and lifestyle characteristics in the exposed and unexposed group. These covariates proved to have significant individual predictive value (data not shown), which was in accordance with our previous similar studies. However, unavailable and thus unmeasured potential confounders such as alcohol consumption status, diet and physical exercise status need to be taken into account when interpreting the results of this study.

Furthermore, we did not have information on the duration and dosage of use, and subjects may, in theory, have been exposed to eye drops prescribed prior to the study period, or even to eye drops prescribed to a family member. Lastly, we only had information on redeemed prescriptions of antazoline-naphazoline in the study period, using this as a proxy for exposure to the drug. Whether the subjects actually used the eye drops remains unresolved, potentially leading to overestimation of antazoline-naphazoline exposure (Olesen et al. 2001). Our study focus was confined to first-trimester exposure to antazoline-naphazoline eye drops, that is the period regarded as critical for organogenesis. Our study does not provide information on the potential risks of abortion, pre-term delivery, low birth weight or small-for-gestational-age infants. Even though we analysed the risk of malformations both in general and within subgroupings, there remains the small risk of missing a small increased risk of malformations with a very low prevalence, for example, neural tube defects, spina bifida and transverse limb deficiencies, previously found in a large-scale epidemiologic study of antihistamine-exposed offspring (Gilboa et al. 2009). Future studies are warranted in the investigation of congenital malformations in stillbirths, as our analyses only apply to live-born offspring.

In conclusion, exposure to antazoline-naphazoline eye drops in the first trimester of pregnancy appears not to be associated with increased teratogenic risk.

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