EXTENDED SPECTRUM PENICILLINS REDUCE THE RISK OF OMPHALOCELE

A population-based case-control study

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Abstract

Background

Omphalocele is a major congenital anomaly associated with significant morbidity and mortality. Regardless, the influence of maternal use of prescription drugs on the risk of omphalocele has only been addressed in a handful of studies. The aim of this study was to assess the influence of maternal risk factors and prescription drugs in early pregnancy on the risk of omphalocele.

Methods

We performed a nationwide register-based case-control study in Finland. The analysis is based on the Finnish Register of Congenital Malformations and Drugs and Pregnancy databases, both upheld by the Finnish Institute for Health and Welfare. All omphalocele cases were identified between Jan 1, 2004 and Dec 31, 2014. Five age-matched controls from the same geographical region were randomly selected for each case. The main outcome measures were maternal risk factors for omphalocele. Our analysis compared the maternal characteristics and the use of prescription drugs during the first trimester of pregnancy between case and control mothers.

Results

Mothers of 359 omphalocele cases were compared with 1738 randomly selected age and area-matched mothers of healthy infants between 1 January 2004 and 31 December 2014. Both maternal obesity (BMI ≥30) and diabetes increased the risk for omphalocele, and their co-occurrence accumulated this risk (aOR 5.06, 95% CI 1.19–21.4). Similarly, history of multiple miscarriages was an independent risk factor (2.51, 1.16–5.43). The oral use of extended spectrum penicillins during the first trimester of pregnancy had a significant, protective influence (0.17, 0.04–0.71). These analyses were adjusted for sex, parity and risk factors reported above. No significant changes in risk were observed with any other medication used during the first trimester.

Conclusion

In conclusion, these findings may suggest that extended spectrum penicillins in the first trimester reduce the risk of omphalocele formation. Additionally, consistent with earlier studies, previous repeated miscarriages, maternal obesity and diabetes were significant risk factors for omphalocele.

Keywords: Exomphalos; Maternal Obesity; Nulliparity; Omphalocele; Risk Factors

Level of Evidence: III (case-control study)

1. INTRODUCTION

Omphalocele, also known as exomphalos, is a rare, congenital abdominal wall defect, where the abdominal contents including intestines and in larger defects, the liver, protrude into the umbilical cord. The reported prevalence of omphalocele varies markedly from 0.74 to 5.13 per 10,000 live births, with no significant long-term trends in prevalence observed [1-3]. The development of the ventral body wall is an intricate process where the epithelium fuses in the midline, leaving only umbilical vessels in the region of the umbilical ring by the tenth week of gestation [4,5]. There are a number of theories, but no consensus on the embryologic basis of the development of omphalocele [5-11]. According to different hypotheses, omphalocele may develop either before or after the physiologic herniation of bowel at 6 to 10 weeks of gestation [12,13]. Omphalocele is often associated with other severe anomalies and chromosomal abnormalities for which over half of the families in the western countries, including Finland, opt for the termination of pregnancy following an antenatal diagnosis [14-16].

Advanced and very young maternal age are well-recognized risk factors for omphalocele [17,18]. Similarly, prenatal alcohol exposure [19], smoking [19,20], obesity [21], disorders of glycemic control [22], and male gender [23] have been associated with increased risk. However, there are only few studies on the effects of maternal medication on the risk of omphalocele [24-27]. The aim of this study was to assess and identify potential maternal risk factors of omphalocele, and especially to assess the effects of the medications used during the first trimester of pregnancy. We hypothesized that maternal use of prescription drugs during the critical susceptibility window in the first trimester of pregnancy would increase the risk of omphalocele.

2. MATERIAL AND METHODS

The analysis is based on the records of the Finnish Register of Congenital Malformations, the Medical Birth Register, the Register on the Induced Abortions and the Care Register for Health Care, all maintained by the Finnish Institute for Health and Welfare. All information in these registers is double-checked by a medical geneticist. The data on maternal prescription medicine use was obtained from the Register on Reimbursed Drug Purchases upheld by the Finnish Social Insurance Institution (Kela). These registers receive information based on a legally compulsory announcement request on all health personnel in our country. The accuracy and high coverage of these data sources have been validated in multiple national and international investigations [28-31].

2.1 Selection of cases and controls

The diagnoses are coded according to the International Statistical Classification of Diseases and Health Related Problems by the World Health Organization (WHO). We identified all the cases in the register born between January 1, 2004 and December 31, 2014 with relevant codes for omphalocele and included them in the study. Five healthy controls matched for maternal age (±1 year), residency, and time of conception (±1 month) were randomly selected for each case from the Medical Birth Register. For the aborted fetuses, live-born, healthy controls were selected. The initial analysis on maternal medication was done at the 4^{th} level of the Anatomical Therapeutic Chemical (ATC) Classification System by WHO.

2.2 Risk factors

Maternal risk factors in the register were analyzed including BMI, parity, smoking, illnesses and history of miscarriages. Maternal diabetes group contained both type 1 and 2 diabetes diagnosed before conception. Gestational diabetes group included all women with recorded diagnosis of gestational diabetes or abnormal oral glucose tolerance result. Smoking was defined as active smoking during 1st trimester. Maternal weight was recorded at the first prenatal visit 8–10 weeks after conception and categorization was made based on calculated BMI. The data on maternal drug purchases was limited to a time window of one month before conception and the first trimester of pregnancy. Regarding maternal medication, ATC groups with more than 10 exposed mothers among cases were selected for analysis.

2.3 Statistical analysis

Conditional logistic regression was used to evaluate different risk factors. First, univariate models were programmed (Table 1) and a multivariable model was created. Factors for the multivariable models were chosen from either being significant in univariate models ($p \leq 0.05$) or being significant in previous reported studies. After this first step, non-significant factors were removed one-by-one. Subjects with missing background data were excluded from the analyses. Odds ratios (OR) along with adjusted odds ratios (aOR) with 95% confidence intervals (CI) were calculated. As a strong interaction was observed between maternal BMI and both pregestational and gestational diabetes ($p<0.001$), we created a combination variable for the multivariable model. All omphalocele cases were included in initial analysis. All significant risk factors in the univariate models and previously reported risk factors in the literature were selected for a logistic regression model to further evaluate their risk for omphalocele. Created multivariable model was subsequently applied for ‘all’ and ‘non-syndromic’ cases separately. All subjects with incomplete background data were automatically

excluded from the analysis and no attempt to replace missing values was made. A Significance level of $p \leq 0.05$ (two-tailed) was set. Analyses were performed using SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

2.4 Ethical aspects

The approval of the Institutional Review boards at the Finnish Institute of Health and Welfare and Turku University Hospital were obtained before conducting this register study.

3. RESULTS

In total 359 cases of omphalocele were identified and compared with 1,738 matched controls. Our cohort included 116 live births, 230 terminations of pregnancy, and 13 stillbirths. Fifty-seven cases were associated with known syndromes, including Trisomy 18 (n=42), Trisomy 13 (n=9), and Beckwith-Wiedemann (n=6), while 302 were classified as 'non-syndromic' omphalocele. Live birth prevalence in Finland was 1.69 per 10,000 births with no consistent trend over time (p=0.275, Figure 1). Maternal age for omphalocele cases (mean 29.4 years, SD 5.6) was compared with the yearly mean maternal age (28.4 years) in Finnish population.

In univariate analysis, nulliparity was a significant risk factor for omphalocele, OR 1.46 (95% CI: 1.15, 1.86). There were 226 (12.7%) obese mothers (BMI ≥30) in our cohort and obesity was associated with a higher risk of omphalocele, OR 2.03 (95% CI: 1.21, 3.42). Both pregestational and gestational diabetes also increased the risk significantly, OR 3.44 (95% CI: 1.29, 9.56) and OR 1.99 (95% CI: 1.17, 3.39), respectively. Newborns/fetuses with omphalocele were more likely to be male although it did not reach statistical significance, OR

1.27 (95% CI: 0.87, 1.87). (Table 1) However, the oral use of extended spectrum penicillins (WHO's ATC Code J01CA: amoxicillin or pivmecillinam) during the first trimester of pregnancy was associated with a reduced risk of omphalocele, OR 0.44 (95% CI: 0.25, 0.77). Number of previous miscarriages, and smoking had no influence on the risk of omphalocele. No significant changes in risk were observed with the use of non-steroidal anti-inflammatory drugs (M01AB, M01AE), antihistamines (R06AE, R06AX), inhaled steroids (R01AD, R03BA), or hormonal drugs used to treat infertility (G03DA, G03GA, H01CA, H01CC, L02AE). (Table 2)

Multivariable analysis adjusted for risk factors reported in table 3 confirmed the reduced risk associated with extended spectrum penicillins, aOR 0.17 (95% CI: 0.04, 0.71), whereas nulliparity was not significantly associated with increased risk aOR 1.28 (95% CI: 0.82, 2.00). Although previous miscarriages were not associated with increased risk in univariate analysis, a history of two or more miscarriages had a statistically significant association in a multivariable model, aOR 2.51 (95% CI: 1.16, 5.43). Maternal obesity, pregestational and gestational diabetes were both associated with increased risk and their co-occurrence increased the risk further. (Table 3 and Figure 1) The same multivariable model was applied for non-syndromic omphalocele cases providing same significant associations with multiple miscarriages, maternal obesity and diabetes increasing the risk and extended spectrum penicillins reducing the risk. Furthermore, increased risk of non-syndromic omphalocele was also associated with a history of one miscarriage, aOR 1.83 (95% CI: 1.01, 3.32).

4. DISCUSSION

The findings of this study may suggest that extended spectrum penicillins during the first trimester of pregnancy are associated with reduced risk of omphalocele. Additionally, previous repeated miscarriages, diabetes, and maternal obesity suggest an association with increased risk of omphalocele.

According to previous studies, nulliparity is associated with elevated risk of several birth defects, including omphalocele [32-34]. On the other hand, history of multiple births has also been identified as a risk factor for omphalocele [35]. In our cohort, nulliparity appeared to be associated with increased risk of omphalocele. However, in the multivariable model, the risk associated with nulliparity was not statistically significant.

Previous miscarriage has been reported to be associated with an increased risk of omphalocele, and history of multiple miscarriages appears to increase the risk further [36]. As omphalocele is often associated with chromosomal anomalies [24], it is possible that couples with chromosomal rearrangements may be at risk for recurrent miscarriages as well as malformed fetuses [37]. These early reports were supported by our results where multiple miscarriages suggested an increased risk of omphalocele. Interestingly, among non-syndromic cases, a history of one miscarriage was also associated with an elevated risk.

Maternal obesity is a well-established risk factor for omphalocele and also several other birth defects including spina bifida, hypospadias, heart defects, anorectal malformations, limb reductions and congenital diaphragmatic hernia [20,21,38,39]. The mechanism remains

unclear. Substantial evidence provided by both human and animal studies suggest hyperglycemia acting as a primary teratogen, and similar mechanisms may explain the elevated risk of birth defects in obese mothers [21,40,41]. According to our results, both obesity and diabetes are associated with increased risk, and co-occurrence of these risk factors accumulates the risk.

There is also limited evidence, that maternal smoking is a risk factor for omphalocele. According to previous reports, elevated risk has been associated with heavy smoking [19], and second-hand smoke exposure [20]. Paradoxically, Feldkamp et al. found no risk to be associated with active smoking, and no dose-response relationship was observed [20]. In keeping with this, and the results of a German group [27], we also found no increased risk for omphalocele with maternal smoking. Although male sex has previously been reported as a risk factor for omphalocele [23,35,42], the association was not significant in our series.

There are contradictory reports on the association between maternal medication and omphalocele. Selective serotonin reuptake inhibitors appear to increase the risk [25,43], although not according to all published data [44]. There are also limited evidence on the risk of maternal asthma medication [26] and antibiotics [27]. In our series, maternal use of inhaled steroids was not associated with elevated risk of omphalocele, and the use of oral extended spectrum penicillins significantly mitigated the risk both in univariate and multivariable analysis. Previously, maternal febrile illness has been found to be a risk factor for omphalocele [45]. As half of omphalocele cases are born prematurely [16] and chorioamniotic microorganisms are also more likely to be found from women with preterm labor [46], it is possible, that chorioamnionitis could be associated with both prematurity and omphalocele.

Additionally, one dose of amoxicillin given at birth has been found to significantly reduce the prevalence of umbilical hernias in a case-control study on new-born piglets [47]. Hence, we speculate that microbiological factors may play a role in the pathogenesis explaining the protective role of penicillins. Further studies are warranted to explore this association.

4.1 Strengths and limitations of study

The strength of our study was the use of validated, high-quality register data with total population coverage [47]. The main limitations are a relatively small sample size, fewer maternal data collected in the Register of Induced Abortions, and that this study solely relies on the accuracy of register data. However, omphalocele is an obvious congenital anomaly on a new-born, and they are typically reported to the national anomaly register in a highly accurate manner [30]. As the data on maternal medications is based on drug purchases only, a major limitation is caused by the lacking information on indications, dosages and whether the drugs were taken highlighting the importance of further studies to confirm our findings. We believe that lacking data on maternal socioeconomic status is only a minor limitation, as omphalocele does not seem to be associated with lower socioeconomic status [27]. Additionally, chromosomal analysis was not obtained in all aborted cases, which may distort the results among non-syndromic cases. Although the proportion of syndromic omphalocele cases in Finland appears to be low, we speculated in our previous study that there might be some reporting bias involved in the associated diagnoses of aborted fetuses [16].

5. CONCLUSIONS

Previous repeated miscarriages, maternal obesity, and diabetes are independent and significant risk factors for omphalocele, while most of maternal medication and smoking showed no

influence. The observed protective association of extended spectrum penicillins warrants further studies.

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Conflict of Interest

None.

Table 1. Univariate analysis of all analyzed maternal risk factors for omphalocele. Large number of missing values are due to fewer data stored in the register of induced abortions.

	Number of Events		Odds ratio	95% CI
	Cases (n=359)	Controls (n=1738)		
Maternal BMI ≥30	26/122 (21.3%)	200/1662 (12.0%)	2.03	1.21, 3.42
Maternal BMI <18.5	8/122 (6.6%)	58/1662 (3.5%)	1.63	0.66, 4.04
Nulliparity	167/359 (46.5%)	638/1738 (36.7%)	1.46	1.15, 1.86
Smoking	17/128 (13.6%)	243/1703 (14.3%)	0.92	0.50, 1.70
Previous miscarriage (1)	65/344 (18.9%)	304/1738 (17.5%)	1.14	0.83, 1.57
Previous miscarriages (≥2)	35/344 (10.2%)	129/1738 (7.4%)	1.52	1.00, 2.31
Pregestational diabetes	6/130 (4.6%)	39/1738 (2.2%)	3.44	1.29, 9.56
Gestational diabetes	22/130 (16.9%)	200/1738 (11.5%)	1.99	1.17, 3.39
Male sex	76/129 (58.9%)	866/1738 (49.8%)	1.27	0.87, 1.87

Note: All subjects with incomplete background data were automatically excluded from the analysis.

Table 2. Univariate analysis of all analyzed prescription drug exposures in early pregnancy.

	Number of Events		Odds ratio	95% CI
	Cases (n=328)	Controls (n=1656)		
Extended spectrum Penicillins	15 (4.6%)	151 (9.1%)	0.44	0.25, 0.77
Non-steroidal anti-inflammatory drugs	23 (7.0%)	134 (8.1%)	0.87	0.54, 1.41
Inhaled Steroids	17 (5.2%)	95 (5.7%)	0.87	0.50, 1.52
Hormonal drugs for infertility	14 (4.3%)	66 (4.0%)	1.10	0.60, 2.01
Antihistamines	14 (4.3%)	77 (4.7%)	0.94	0.52, 1.70

Note: Includes some missing values among cases and controls.

Table 3. Adjusted odd ratios and 95% CI of the risk factors of omphalocele adjusted for variables presented in this table. Large number of missing values are due to fewer data stored in the register of induced abortions.

	Number of Events		Adjusted odds ratio	95% CI
	Cases (n=359)	Controls (n=1656–1738)		
Extended spectrum Penicillins	15/328 (4.6%)	151/1656 (9.1%)	0.17	0.04, 0.71
Nulliparity	167/359 (46.5%)	638/1738 (36.7%)	1.28	0.82, 2.00
Male sex	76/129 (58.9%)	866/1738 (49.8%)	1.35	0.89, 2.07
Previous miscarriage (1)	65/344 (18.9%)	304/1738 (17.5%)	1.53	0.86, 2.72
Previous miscarriages (≥2)	35/344 (10.2%)	129/1738 (7.4%)	2.51	1.16, 5.43
Pregestational diabetes or maternal obesity	21/122 (17.2%)	188/1662 (11.3%)	1.79	1.01, 3.17
Pregestational diabetes and maternal obesity	5/122 (4.1%)	25/1662 (1.5%)	5.06	1.19, 21.4
Gestational diabetes or maternal obesity	29/122 (23.8%)	247/1662 (14.9%)	1.92	1.10, 3.36
Gestational diabetes and maternal obesity	9/122 (7.4%)	75/1662 (4.5%)	2.47	1.08, 5.66

Note: All subjects with incomplete background data were automatically excluded from the analysis.

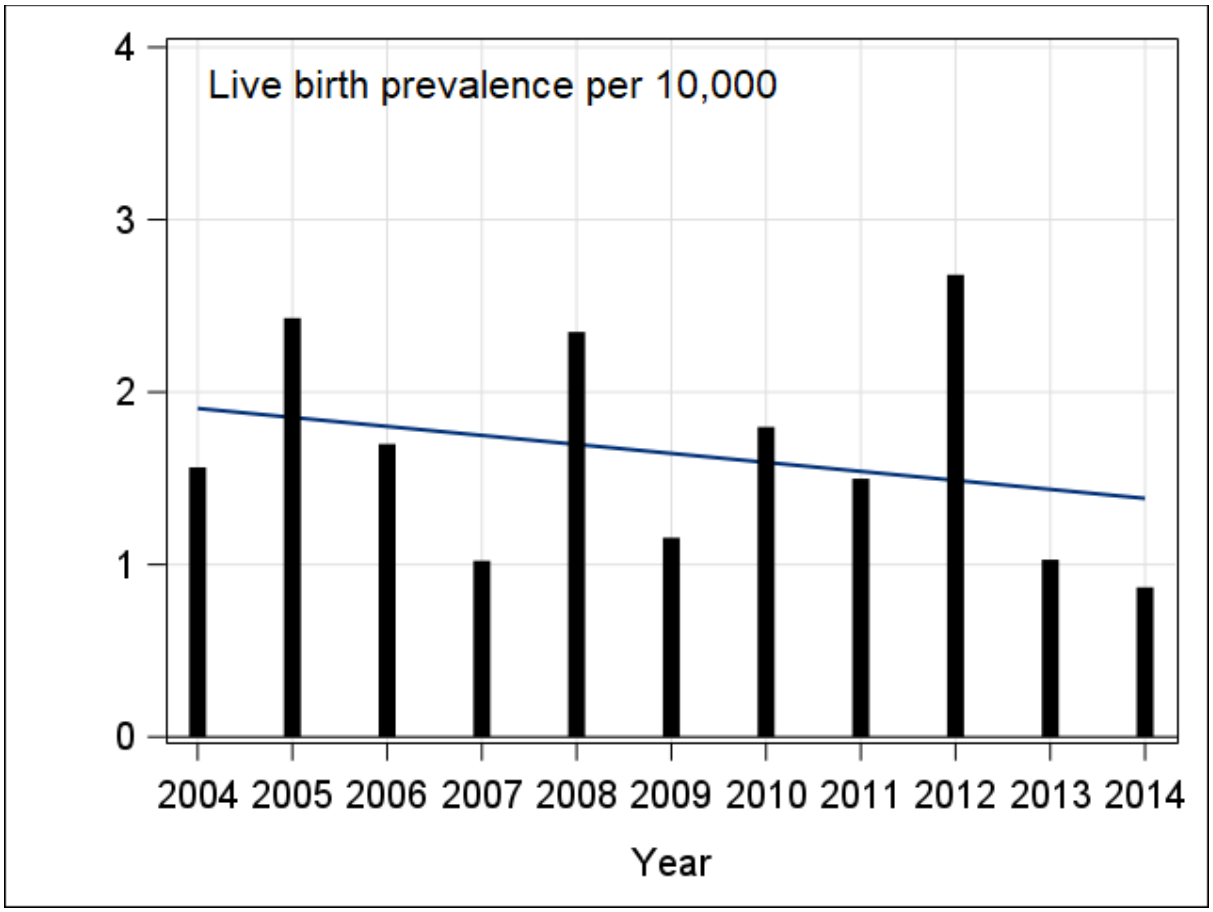

Figure 1. No significant change was seen in live birth prevalence of omphalocele (p=0.275).

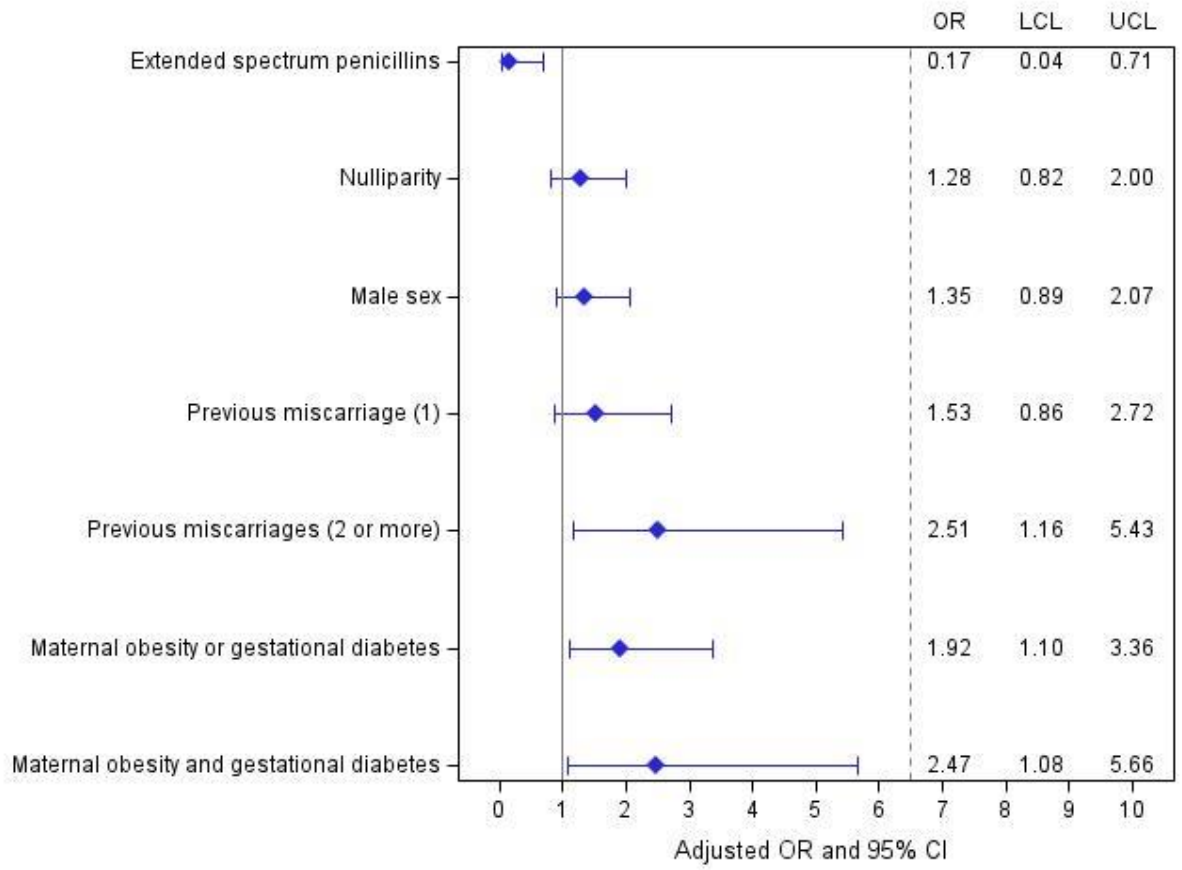

Figure 2. Multivariable analysis of the risk factors adjusted for variables presented in the figure along with adjusted odds ratios and 95% CI.

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