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EXTENDED SPECTRUM PENICILLINS DURING THE FIRST TRIMESTER OF PREGNANCY REDUCE THE RISK OF OMPHALOCELE

A population-based case-control study

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Abstract

Objectives

To assess the influence of maternal risk factors and prescription drugs in early pregnancy on the risk of omphalocele.

Design

A population-based case-control study.

Setting

Nationwide cohort based on the Finnish Register of Congenital Malformations and Drugs and Pregnancy databases.

Participants

Mothers of 359 omphalocele cases were compared with 1 738 randomly selected age-matched mothers of healthy infants between 1 January 2004 and 31 December 2014.

Main outcome measures

The main outcome was a new-born/foetus with omphalocele. Our analysis compared the characteristics and the use of prescription drugs in early pregnancy between case and control mothers.

Results

Both maternal obesity (BMI ≥30) and diabetes increased the risk for omphalocele, and their co-occurrence accumulated the risk. Similarly, history of multiple miscarriages was an independent risk factor (2·51, 1·16–5·43). However, the oral use of extended spectrum penicillins during the first trimester of pregnancy had significant, protective influence (0·17, 0·04–0·71). No significant changes in risk were observed with any other medication used during the first trimester.

Conclusions

Extended spectrum penicillins significantly mitigated the risk of omphalocele; a novel finding which warrants further studies. Our findings were consistent with earlier studies confirming previous repeated miscarriages, obesity and diabetes as risk factors for omphalocele. Other maternal medication and smoking had no influence on the risk of omphalocele.

Author contributions

Study conception and design: Helenius, Hyvärinen, Raitio, Tauriainen
Acquisition of data: Leinonen, Gissler, Syvänen, Helenius, Raitio, Tauriainen, Sankilampi
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Drafting of manuscript: Raitio
Critical revision: All authors

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 in 10,000 live births, with no significant long-term trends in prevalence observed.[1-3] 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.[4-6]

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.[7, 8] There are a number of theories, but no consensus on the embryologic basis of the development of omphalocele.[8-14] According to different hypotheses, omphalocele may develop either before or after the physiologic herniation of bowel at 6 to 10 weeks of gestation.[15, 16] Regardless, the critical susceptibility window is during the first trimester of pregnancy.

Advanced or very young maternal age is a well-recognized risk factor for omphalocele.[17, 18] Similarly, prenatal alcohol exposure[19], smoking[19, 20], obesity[21], disorders of glycaemic 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 safety and effects of the medications used during the first trimester of pregnancy. We hypothesized that maternal exposures during the first trimester of pregnancy would affect the risk of omphalocele.

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. 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 data on maternal drug purchases was limited to a time window of one month before conception and the first trimester of pregnancy. The accuracy and high coverage of these data sources have been validated in multiple national and international investigations.[28-31]

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 foetuses, live-born, healthy controls were selected. The initial analysis on maternal medication was done at the 4th level of the Anatomical Therapeutic Chemical (ATC) Classification System by WHO.

Maternal risk factors in the register were analysed 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. Regarding prescription medicine use, we initially identified and selected drug groups with higher frequency among cases of abdominal wall defects. Subsequently, ATC groups with more than 10 events among cases, were selected for further analysis.

Conditional logistic regression was used to evaluate different risk factors. First, univariate models were programmed (Table 1) and a multivariable model was created. 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. A Significance level of $p\leq0.05$ (two-tailed) was set. Analyses were performed using SAS System, version 9·4 for Windows (SAS Institute Inc., Cary, NC, USA).

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.

Results

In total 359 cases of omphalocele were identified and compared with 1738 matched controls. Birth prevalence in Finland was 1·96 per 10,000 births with no consistent trend over time. Maternal age for omphalocele cases was comparable with mean maternal age 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 (2·03, 1·21–3·42). Both pregestational and gestational diabetes also increased the risk significantly, (3·44, 1·29–9·56) and (1·99, 1·17–3·39), respectively. New-borns/foetuses with omphalocele were more likely to be male although it did not reach statistical significance (1·27, 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 (0·44, 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)

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. Multivariable analysis confirmed the reduced risk associated with extended spectrum penicillins (0·17, 0·04–0·71), whereas nulliparity was not significantly associated with increased risk (1·28, 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 (2·51, 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)

	Number of Events		Odds ratio (95% CI)
	Cases (n=122–359)	Controls (n=1662–1738)	
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)

Table 1. Univariate analysis of all analysed 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=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)

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

	Number of Events		Adjusted odds ratio (95% CI)
	Cases (n=122–359)	Controls (n=1662–1738)	
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)

Table 3. Adjusted odd ratios and 95% CI of the risk factors of omphalocele

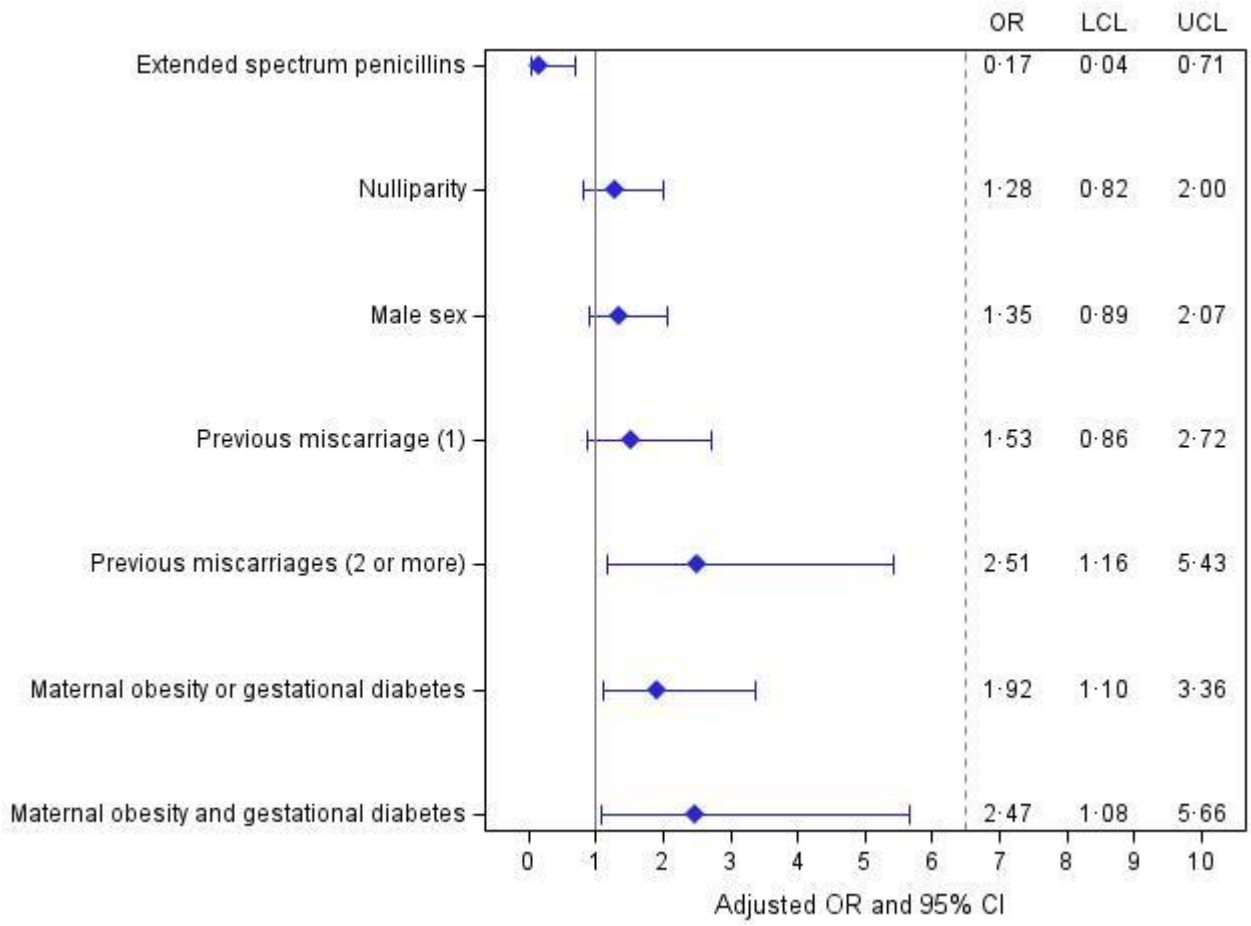

Figure 1. Multivariable analysis of the risk factors along with adjusted odds ratios and 95% CI.

Discussion

We have demonstrated that extended spectrum penicillins during the first trimester of pregnancy are associated with significantly reduced risk of omphalocele. Additionally, previous repeated miscarriages, diabetes, and maternal obesity are independent risk factors for omphalocele.

Comparison with other studies

There are contradictory reports on the association between maternal medication and omphalocele. Selective serotonin reuptake inhibitors appear to increase the risk[25, 32], although not according to all published data.[33] 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.[34] As half of omphalocele cases are born prematurely[6] and chorioamniotic microorganisms are also more likely to be found from women with preterm labor[35], 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.[36] 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.

Our findings were consistent with those of Campaña et al. who reported increased risk of omphalocele in mothers with previous repeated miscarriages.[37] In accordance with our results, they also found that those with more than one miscarriage have even higher risk. 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.[38] According to previous reports, nulliparity is associated with elevated risk of several birth defects, including omphalocele.[39, 40] Our univariate analysis provided similar results, but in the multivariable model, the risk associated with nulliparity was not statistically significant.

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, 41, 42] The mechanism remains unclear. Substantial evidence provided by both human and animal studies suggest hyperglycaemia acting as a primary teratogen, and similar mechanisms may explain the elevated risk of birth defects in obese mothers.[21, 43, 44] 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, 45, 46] the association was not significant in our series.

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 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] 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]

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.

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