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RISK FACTORS AND PREVALENCE OF LIMB DEFICIENCIES ASSOCIATED WITH AMNIOTIC BAND SEQUENCE

A population-based case-control study

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Abstract

Background

Limb deficiencies associated with amniotic bands comprise a wide range of congenital anomalies. The association of maternal medication and the risk of amniotic band sequence (ABS) has not yet been addressed.

Methods

A nationwide population-based case-control study using national registers on congenital anomalies, births and induced abortions, cross-linked with information on maternal prescription medicine use obtained from the registers on Reimbursed Drug Purchases and Medical Special Reimbursements. All cases with congenital limb deficiency associated with amniotic bands born between 1996 and 2008 were included in the study. Five controls without limb deficiency matched for residency and time of conception were randomly selected from the Medical Birth Register.

Results

In total, 106 children with limb deficiency associated with ABS were identified and compared with 530 matched controls. Young maternal age (<25 years) increased the risk of limb deficiencies, OR 1.72 (95% CI: 1.06, 2.80). Primiparity was also associated with increased risk, aOR 2.42 (95% CI: 1.52, 3.88). After adjusting for maternal age, pregestational diabetes, and parity, maternal use of beta blockers, aOR 24.2 (95% CI: 2.57, 228) and progestogens, aOR 3.79 (95% CI: 1.38, 10.4) during the first trimester of pregnancy significantly increased the risk of limb deficiencies associated with amniotic bands.

Conclusion

Primiparity significantly increased the risk of limb defects associated with amniotic bands. Also, a novel association on increased risk of ABS with maternal use of progestogens or beta blockers during the first trimester of pregnancy was observed.

Level of Evidence: III

Introduction

Amniotic band sequence, or amniotic band syndrome (ABS), or amnion rupture sequence (ARS) is the term applied to a wide range of congenital anomalies (constriction rings associated with fibrous bands, limb and digital amputations, and cutaneous and visceral abnormalities).[1,2] In the study of Lowry et al.[2] amniotic bands with limb deficiency was the most frequent phenotype. There are two theories for the pathogenesis: the intrinsic causes (defect of germ plasm, vascular disruption and disturbance of threshold boundaries of morphogens during gastrulation) or the extrinsic causes (amniotic band rupture).[1,3] The proposed pathogenesis for primary disruption of amniotic bands is that occlusion of a developing limb causes necrosis at the terminus, which adheres to and pulls off strips of amnion, resulting in mechanical damage to the fetus, such as constriction bands and clefts.[4]

Only a few reports on the prevalence of ABS with limb deficiencies exist. A population-based study from Australia reported an incidence of 2.03 per 10 000.[5] This included middle trimester terminations and amniotic bands without limb deficiency. A South American group [6], on the other hand, reported birth prevalence of 0.89 per 10 000 births for ADAM (amniotic deformity, adhesions, mutilations). Orioli et al.[6] also reported that 11% of their ADAM sequence cases were stillborn and 15% died during neonatal period.

Many risk factors have been associated with amniotic band sequences with or without body wall defects. Young maternal age has been found to be associated with ARS.[4,7] Similarly, early reports have also identified primiparity as a risk factor for ABS.[1,4,7] Werler et al.[4] reported increased risk with the use of aspirin for limb reduction defects accompanied by amniotic

bands. Also, the use of acetaminophen in early pregnancy has been reported to be a risk factor for ARS.[7] To the best of our knowledge, these are the only published studies to date on the association of maternal medication and the risk of ABS.

The aim of this study was to explore maternal and pregnancy related risk factors for congenital limb deficiencies associated with amniotic bands. We hypothesized that first trimester medication use would increase the risk of congenital limb deficiencies.

Methods

All cases (n=106) with congenital limb deficiencies associated with amniotic bands born in Finland between Jan 1, 1996 and Dec 31, 2008 were identified from the National Register of Congenital Malformations, the Medical Birth Register and the Register on the Induced Abortions, all maintained by the Finnish Institute for Health and Welfare. Information on maternal prescription medicine use was obtained from the Register on Reimbursed Drug Purchases and the Register on Medical Special Reimbursements (Social Insurance Institution of Finland). These registers include data on all reimbursed drug purchases. This data was limited to include drug purchases in the time window of one month prior to conception and the first trimester of pregnancy and exposure was defined as a reimbursed drug purchase in this time window. These registers receive information based on a legally compulsory announcement request on and have been validated confirming accurate data with high coverage.[8-10]

A detailed description of the data collection for congenital limb deficiencies has been given in previous papers.[11,12] All cases with ICD-9 codes 75XX and 65XX were identified and reviewed. Identified matches were checked by the principal investigators and all cases other than congenital limb deficiencies due to amniotic bands were excluded. Live births, stillbirths, and fetuses from spontaneous abortions and terminations of pregnancy due to fetal anomalies were included.

Five controls without limb deficiencies from the Medical Birth Register matched for residency, and time of conception (± 1 month) were randomly selected for each case. For the terminated fetuses, live-born controls without a limb anomaly were selected.

Potential maternal risk factors in the register were analyzed including maternal age, BMI, parity, smoking, documented long-term diseases from Medical Special Reimbursements (Diabetes Mellitus, Asthma, Psychotic Mental Conditions, Depression, Epilepsy, and Inflammatory Bowel Diseases), history of miscarriages, and utilization of assisted reproductive technology (ART). Smoking was defined as active smoking during 1st trimester. Maternal weight was recorded at the first prenatal visit 8–10 weeks after conception. The initial analysis on maternal medication was done at the 4th level of the Anatomical Therapeutic Chemical (ATC) Classification System by WHO. All analyzed drug groups are given in an annex. Each drug group with at least five exposed mothers was studied in univariate logistic regression and significant risk factors in these analyses were included the multivariable model.

Conditional logistic regression was used to evaluate different risk factors. First, univariate models were programmed, and Fisher's exact test was executed to search potential risk factors. Subsequently, a multivariable model was created. Odds ratios (OR) along with adjusted odds ratios (aOR) with 95% confidence intervals (CI) were calculated. The 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 study.

Results

There were 106 cases of congenital limb deficiencies associated with amniotic bands including five (4.7%) stillbirths and 38 (35.8%) elective terminations of pregnancy. Total prevalence was 1.12 per 10,000 births and live birth prevalence was 0.67 per 10,000 live births. Four infants with ABS died during the first week of life and there was also one additional death during the first year of life. The perinatal mortality rate was 132 per 1,000 births and the infant mortality rate was 79 per 1,000 live births.

The 106 cases with limb deficiency associated with amniotic bands were identified and compared with 530 matched controls. In univariate analyses, young maternal age (<25 years, OR 1.72 (95% CI: 1.06, 2.80) and primiparity OR 2.56 (95% CI: 1.65, 3.97), were identified as significant potential maternal risk factors for congenital limb deficiencies associated with amniotic bands. Infants with ABS were more likely to be born prematurely, OR = 17.4, 95% CI

9.62, 31.4. Other maternal risk factors were not significantly associated with increased risk (Table 1). Maternal illnesses were not significantly associated with increased risk of limb deficiencies.

Multivariable analysis adjusted for maternal age and pregestational diabetes confirmed the increased risk associated with primiparity (aOR = 2.42, 95% CI: 1.52, 3.88). The multivariable analysis on maternal prescription drugs was adjusted for maternal age, primiparity and pregestational diabetes and beta blockers (ATC code C07A) and progestogens (ATC code G03D) were both associated with significantly increased risk of ABS (aOR = 24.2, 95% CI: 2.57, 228 and aOR = 3.79, 95% CI: 1.38, 10.4 respectively – (Table 2).

Discussion

In this large population-based case-control study we have demonstrated a novel finding on the increased risk of first trimester use of beta blockers and progesterone on limb deficiencies associated with amniotic bands. ABS was also associated with primiparity and young maternal age.

Our data on exposures and outcomes were prospectively collected by the universally accessible healthcare system of our country. The registers used in this study were complete with accurate data and the coverage of the data on children with congenital limb deficiency associated with amniotic bands during the study years is high.[8-13] The diagnosis of each congenital limb deficiency case associated with amniotic bands was confirmed by the principal investigators and the controversial cases were discussed by two experienced

pediatric orthopedic surgeons. The case-control design was selected to identify risk factors for very rare clinical conditions.

Orioli et al.[6] reported that unspecified maternal drug use was a risk factor to ADAM sequence. We found associations with beta blockers and progesterone. This risk associated with beta blockers was 24-fold on the limb deficiencies associated with amniotic bands. There are no previous reports on associations between beta blockers and limb deficiencies. Also, an international cohort study found maternal beta blocker use to be safe during pregnancy with no increased risk of congenital malformations.[14] In the literature there are reports of maternal pre-eclampsia and chronic hypertension in patients with limb deficiencies.[15-17] Our findings on the beta blockers support the hypothesis that amniotic band syndrome associated limb deficiency might be related to changes in the fetal microvascular system.[4] However, also maternal hypertension has been associated with increased risk of congenital malformation[18] making it difficult to assess whether the risk is associated with the medication or hypertension itself.

Current data showed an association with progestogens and limb deficiencies associated with amniotic bands. There are early reports on maternal use of exogenous sex hormones and associations of various congenital malformations including limb deficiencies.[19-21] Other reports have not found significant associations.[22] Recent prospective observational cohort study found no association between major birth defects and oral contraceptives.[23] Most cases in our research had natural progestogens code which is often used with ART. Based on our research it is impossible to say if it is the hormone itself, the technology used, or the maternal

and paternal factors related to subfertility that cause the positive correlation with congenital limb deficiencies. Previous studies have also had the same challenge.[24]

Several studies have reported a positive association with active smoking and amniotic band sequence-limb-body-wall-complex (ABS-LBWC)[4,25,26] and one study found significant positive association with secondhand smoking.[27] Our results also suggested that smoking would be associated with increased risk, but the association was not statistically significant. Also, our study was limited by lacking data on maternal smoking in the Register of Induced Abortions.

Previous studies have reported twofold increase in the risk of ABS associated with young maternal age.[5,28] Werler et al.[7] observed a threefold increase in ABS among mothers <25 years of age. However, this association was not statistically significant. Similar, borderline significant results were also reported by Orioli et al.[6] Our findings support previous results regarding young maternal age as a risk factor for ABS.

Our results were consistent with early reports regarding the increased risk of limb deficiencies associated with amniotic bands among primiparous women.[1,4,7] Besides ABS, primiparity has been previously identified as a risk factor for several other birth defects including diaphragmatic hernia, omphalocele, and gastroschisis.[29,30] It has been postulated, that biologic or environmental factors associated with primiparity could explain these associations. However, the underlying mechanism remains unclear.[29]

The main limitations are a relatively small sample size. The primary aim of the Drugs and Pregnancy database is to identify potential teratogenic agents. As the data on maternal

medications is based on reimbursed drug purchases, and the information on indications, dosages and possible use of over-the-counter medications is lacking. However, almost all prescription-only drugs necessary for treatment of an illness are reimbursable in Finland including over-the-counter drugs when prescribed by a physician. Nevertheless, lacking data on over-the-counter medications could explain, why exposures to previously reported risk factors aspirin and acetaminophen were too few to be included in statistical analyses.

Children born with amniotic band syndrome are rare and these parents often seek answers why their child developed this condition. The results of the current study provide additional insights into these questions. In conclusion, a novel finding on the increased risk of ABS associated with maternal use of progestogens and beta blockers was observed. Future studies are warranted to confirm these associations. Early reports on the increased risk of ABS associated with primiparity and young maternal age were supported by our results.

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Table 1. Maternal and fetal characteristics and their association with congenital limb deficiencies associated with amniotic bands.

	Number of Events		Odds ratio	95% CI
	Cases (n=106)	Controls (n=530)		
Maternal Age < 25 years (ref 25 – 34)	33 (31.1%)	111 (20.9%)	1.72	1.06, 2.80
Maternal Age ≥ 35 years (ref 25 – 34)	11 (10.4%)	67 (12.6%)	0.92	0.45, 1.86
Primiparity	70 (66.0%)	228 (43.0%)	2.42	1.52, 3.88
Pregestational diabetes	2 (1.9%)	2 (0.4%)	5.08	0.71, 36.5
Maternal chronic hypertension	2 (1.9%)	2 (0.4%)	10.2	0.91, 113.6
Assisted reproductive technology	3 (2.8%)	11 (2.1%)	2.50	0.63, 10.0
Smoking	18 (17.0%)	90 (17.0%)	1.61	0.88, 2.94
Multiple pregnancy	4 (3.8%)	22 (4.2%)	0.91	0.31, 2.67
Invasive fetal investigation	4 (3.8%)	18 (3.4%)	1.46	0.46, 4.57
Prematurity	59 (55.7%)	33 (6.2%)	17.4	9.62, 31.4
Male Sex	52 (49.1%)	260 (49.1%)	1.03	0.67, 1.58

Table 2. Multivariable analysis adjusted for maternal age, primiparity and pregestational diabetes of maternal risk factors for congenital limb deficiencies associated with amniotic bands.

Exposure (ATC code)	Number of Events		Adjusted Odds ratio	95% CI
	Cases (n=106)	Controls (n=530)		
Beta blockers (C07A)	4 (3.8%)	1 (0.2%)	24.2	2.57, 228.2
Progestogens (G03D)	7 (6.6%)	11 (2.1%)	3.79	1.38, 10.4
Gonadotropins (G03G)	3 (2.8%)	11 (2.1%)	1.46	0.39, 5.45
Muscle relaxants (M03B)	2 (1.9%)	3 (0.6%)	4.39	0.36, 53.1

ATC code	Name of the drug group
A02B	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE
A03F	PROPULSIVES
A07E	INTESTINAL ANTIINFLAMMATORY AGENTS
A10A	INSULINS AND ANALOGUES
B01A	ANTITHROMBOTIC AGENTS
C07A	BETA BLOCKING AGENTS
D01A	ANTIFUNGALS FOR TOPICAL USE
D06B	CHEMOTHERAPEUTICS FOR TOPICAL USE
D07A	CORTICOSTEROIDS, PLAIN
D10A	ANTI-ACNE PREPARATIONS FOR TOPICAL USE
G01A	ANTIINFECTIVES AND ANTISEPTICS, EXCL. COMBINATIONS WITH CORTICOSTEROIDS
G03C	ESTROGENS
G03D	PROGESTOGENS
G03G	GONADOTROPINS AND OTHER OVULATION STIMULANTS
H01C	HYPOTHALAMIC HORMONES
H02A	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
H03A	THYROID PREPARATIONS
J01A	TETRACYCLINES
J01C	BETA-LACTAM ANTIBACTERIALS, PENICILLINS
J01D	OTHER BETA-LACTAM ANTIBACTERIALS
J01F	MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
J01M	QUINOLONE ANTIBACTERIALS
J02A	ANTIMYCOTICS FOR SYSTEMIC USE
L02A	HORMONES AND RELATED AGENTS
M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
M03B	MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS
N02B	OTHER ANALGESICS AND ANTIPYRETICS
N02C	ANTIMIGRAINE PREPARATIONS
N03A	ANTIEPILEPTICS
N05A	ANTIPSYCHOTICS
N05B	ANXIOLYTICS
N06A	ANTIDEPRESSANTS

P01A	**AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISEASES**
R01A	**DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE**
R01B	**NASAL DECONGESTANTS FOR SYSTEMIC USE**
R03A	**ADRENERGICS, INHALANTS**
R03B	**OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS**
R05D	**COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS**
R05F	**COUGH SUPPRESSANTS AND EXPECTORANTS, COMBINATIONS**
R06A	**ANTIHISTAMINES FOR SYSTEMIC USE**
S01G	**DECONGESTANTS AND ANTIALLERGICS**

Annex: List of all analyzed ATC drug groups with exposures among case or control mothers.