AUTHOR	Raitio A, Tauriainen A, Syvänen J, Kemppainen T, Löyttyniemi E, Sankilampi U, Vanamo K, Gissler M, Hyvärinen A, Helenius I
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OMPHALOCELE - TRENDS, PREVALENCE, MORTALITY AND ASSOCIATED MALFORMATIONS

A population-based study

Arimatias Raitio[1], Asta Tauriainen, Johanna Syvänen[1], Teemu Kemppainen[3], Eliisa Löyttyniemi[3], Ulla Sankilampi[4], Kari Vanamo[2], Mika Gissler[5,6], Anna Hyvärinen[7], Ilkka Helenius[1]

1. Department of Paediatric Surgery and Orthopaedics, Turku University Hospital and Turku University, Turku, Finland
2. Department of Paediatric Surgery, Kuopio University Hospital, Kuopio, Finland
3. Department of Biostatistics, University of Turku and Turku University Hospital, Turku, Finland
4. Department of Paediatrics, Kuopio University Hospital, Kuopio, Finland
5. Information Services Department, Finnish Institute of Health and Welfare, Helsinki, Finland
6. Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Stockholm, Sweden
7. Department of Paediatric Surgery, Tampere University Hospital and Tampere University, Tampere, Finland

Abstract

Aim of the Study

To assess the changes in prevalence, mortality and termination pregnancy of omphalocele, and to identify associated anomalies.

Methods

A population-based nationwide register study. All cases with omphalocele were identified in the Finnish Register of Congenital Malformations and the Care Register for Health Care from 1993 to 2014 including live births, stillbirths, and terminations of pregnancy due to fetal anomalies. Associated anomalies were recorded, and analyzed, and perinatal and infant mortality and prevalence were calculated.

Results

There were 600 cases with omphalocele including 229 live births, 39 stillbirths and 332 (55%) abortions. Birth prevalence in Finland was 1.96 per 10,000 births with no consistent trend over time. However, total prevalence was much higher (4.71/10,000) because more than half of these families choose option for termination of pregnancy. Omphalocele is often complicated with other anomalies; most commonly chromosomal abnormalities (9.3%), heart defects (6.3%), central nervous system anomalies (3.0%), gastrointestinal and urogenital malformations (both 2.0%). Proportion of chromosomal and central nervous system abnormalities were even higher in those pregnancies that are terminated. Overall infant mortality was 22%. One-year survival rates for isolated omphalocele, cases with multiple anomalies and neonates with chromosomal defects were 80%, 88% and 17% respectively.

Conclusion

Omphalocele is a rare congenital anomaly, often associated with other malformations. Our data suggest that isolated cases may be more common than previously thought. In the absence of chromosomal defects, survival is reasonably good. Regardless, more than half of these pregnancies are often terminated.

Introduction

Omphalocele or exomphalos is a relatively uncommon congenital anomaly. In omphalocele abdominal organs are herniated through an open umbilical ring and the defect is covered by membranes. It is often associated with other severe anomalies including chromosomal abnormalities and cardiac defects and overall mortality ranges from 15.6 to 52.4%.[1-4] In isolated cases, survival rates of over 90% have been reported while only one fourth of those with chromosomal abnormalities, survives the first year.[5] The prevalence of omphalocele is 0.74-5.13 in 10 000 live births and no long term trends or changes in occurrence have been observed.[6-8] However, one US study reported a modest, yet statistically not significant, decrease in prevalence, and also improvement in survival over their 10 year study period.[9]

Most of the cases are picked up in prenatal ultrasound screening with reported detection rates as high as 96%.[10] As many of these fetuses are also diagnosed with other associated anomalies or chromosomal abnormalities, over half of the families in the western countries opt for the termination of pregnancy.[10-12] In the Netherlands, the abortion rate has nearly doubled since the introduction of their prenatal screening program.[10] With high abortion rates, elevated risk of intrauterine fetal demise and high perinatal mortality, less than 10% of antenatally detected omphalocele cases reach the stage of operative repair.[9,10,13] In Finland, every pregnant woman is entitled to have two antenatal ultrasound scans during pregnancy; first scan between 11 and 13 weeks of pregnancy and the second in 19 – 21 weeks of gestation.[14] All omphalocele cases are treated at one of our five tertiary pediatric surgery centers (Table 1) and antenatally detected cases are delivered at the unit.

Our aim was to assess the prevalence, mortality, and the rates of termination of pregnancy of omphalocele in the Finnish population during the last 20 years, and to identify possible long-term changes in trends and the most commonly associated malformations.

Methods

The analysis is based on the records of the Finnish Register of Congenital Malformations, which contains data on all live births, stillbirths, and terminations of pregnancy due to fetal anomalies. The Finnish Institute for Health and Welfare has maintained the register since 1963, and its main purpose is to continuously monitor the prevalence of congenital anomalies and to identify potential risk factors for fetal defects. The register also receives information from other national health registers including the Medical Birth Register, the Register of Induced Abortions, the Care Register for Health Care, the Register of Visual Impairment and the Cause of Death register collected by Statistics Finland.

The data are collected by using specific “Declaration of Malformation” forms which are received from the maternity and pediatric hospitals. The hospitals may also send the medical records, from which the requested data is abstracted. Before entering the data to the register, the list of diagnosis is obtained and confirmed with the previously mentioned registries and additional information (patient records, radiographs, photographs, specialist consultation etc.) is requested if necessary. All recorded

information is double-checked by a medical geneticist. The coverage and data quality of the register have been considered good in several studies.[15-17] As required by the national legislation, the use of the data was authorized by the Finnish Institute of Health and Welfare.

The diagnoses are coded according to the International Classification of Diseases (ICD) by the World Health Organization – both ninth and tenth revisions (ICD-9 and ICD-10) were used during our study period. We identified all the cases in the register born between 1st of January 1993 to 31st of December 2014 with codes either 75672 (ICD-9) or Q79.2 (ICD-10) for omphalocele and included them in the study. The follow up period was one year.

Statistical tests were performed as two-sided, with a significance level set at $p<0.05$. Continuous variables were summarized with mean and standard deviation (SD). Categorical variables were summarized with counts (n) and percentages. For mortality, odds ratios (with 95% confidence interval) were calculated where possible. Change in livebirth prevalence over years was evaluated with linear regression. The analyses were performed using SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). Birth prevalence and total prevalence are given per 10 000 births, and live birth prevalence is given per 10 000 live births as defined by EUROCAT.[18]

Results

We identified 600 cases with omphalocele in our register search from 1993 to 2014 in Finland. There were 332 (55%) abortions and 268 (45%) births, of which 229 (38%) were live births and 39 (6.5%) stillbirths. Total prevalence (live births, stillbirths and terminations due to anomalies) was 4.71 per 10,000 births. With high number of abortions, however, birth prevalence (live births and stillbirths) and live birth prevalence were much lower; 1.96 and 1.69 in 10,000 respectively (Figure 1). No changes in the abortion rates was observed during our study period. However, termination of pregnancy was significantly more common in the southern parts of Finland ($p=0.03$) (Table 1). On average, these infants tend to be born prematurely (average 36.4 weeks of gestation) and in total, there were 135 (50%) premature babies in our cohort (<38 gestational weeks). Vaginal delivery was favored in most cases (152 vaginal births vs 116 caesarean sections).

Omphalocele is often associated with other major anomalies. In the group of aborted fetuses, the most common associations were chromosomal abnormalities (13%, 44/332) and central nervous system anomalies (4%, 14/332). Congenital heart defects, limb anomalies, congenital diaphragmatic hernia, gastrointestinal and urogenital malformations were all found in 1% (4/332) of the cases. Maternal age was significantly higher in those who opted for termination than in those who continued with pregnancy (mean age 32.0 [SD 6.4] years vs 30.0 [SD 6.0] years, $p<0.001$).

In total, 77% (176/229) of the liveborn omphalocele cases were isolated and 18% (41/229) had multiple anomalies. Aneuploidy was seen only in 5% of cases among those who were born (13/268). Nearly 8%

(21/268) of neonates with omphalocele also had heart defects, and 2% (5/268) had central nervous system anomalies. Beckwith-Wiedemann syndrome, skeletal anomalies, gastrointestinal and urogenital malformations were all found in 3% in our study population (8/268). (Table 2)

At the age of one year, 179 (78%) patients were alive. Hence, the overall infant mortality of omphalocele was 22%, with 82% of deaths occurring in the first 28 days. Interestingly, neonates with multiple anomalies had the best survival (88%), whereas 80% of the isolated cases were alive at the age of one (Table 3). Only 17% of the neonates with chromosomal abnormalities survived the first year. There was no statistically significant difference in the survival between hospitals (Table 1). However, there was a significant decline in the mortality rate during our study period after the first five years (p=0.03) (Table 4).

Maternal diabetes (p=0.45), obesity (OR: 0.93, 95% CI 0.28 to 3.12), smoking (OR: 0.78, 95% CI 0.38 to 1.68), hypertension (p=0.59), and mode of delivery (OR for caesarean: 0.65, 95% CI 0.34 to 1.22) had no impact on the infant mortality.

Discussion

According to previous reports, the worldwide prevalence of omphalocele has remained constant. We found no change in prevalence trend during our study period from 1993 to 2014. Our live birth prevalence (1.69 per 10,000 live births) is in range with other studies.[6-9] Considering our total prevalence of 4.71 per 10,000 births, however, there appears to be a significant increase from the baseline prevalence of 1.96 per 10,000 births in the 1970s in Finland; in the era before antenatal ultrasound screening and terminations of pregnancy due to fetal anomalies.[19,20] Similar trend has also been observed in the UK comparing the data from 2005 to 2011 with previous reports. In 20 years, the birth prevalence of omphalocele increased from 0.77 to 3.8 per 10.000 live births.[5,21]

Omphalocele is complicated with other organ anomalies and chromosomal abnormalities in 27-88% of the cases.[9,10,22,23] In our study population, however, the number of isolated cases was higher than generally reported (77%). Only 8% of the neonates had heart defects, which is in the lower range with other studies reporting cardiac anomalies in 7-50% of the patients.[9,24-26] Our series also had a reasonably low number of abnormal karyotypes in both aborted fetuses (13%) and neonates (5%) comparing with 17-49% aneuploidy rates in other reports.[9,10,27]

Due to a considerable risk of associated abnormalities, the abortion rates for omphalocele exceed 50% in many western countries.[10,11,27] The proportion of terminations (55%) in Finland was comparable with other reports. Even though the maternal age was not found to be a significant risk factor for omphalocele, the mothers opting for termination were considerably older (mean age 32.0 [SD 6.4] years vs 30.0 [SD 6.0] years, p<0.001). It has been speculated that older women may feel more pressured to undergo the antenatal examinations and act according to the findings.[28] Older women may also have greater concerns with potential offspring health.[29] Interestingly, a similar trend was seen in our

gastroschisis cohort as well.[30] Consistent with earlier reports, we also had the highest rates of abortions in the most densely populated and urban areas of Finland.[31,32]

Co-occurring chromosomal defects and organ anomalies are the best predictors of mortality in omphalocele.[5,9] Our overall mortality of 22% is well in range with other reports (15-54%).[1-4,9] One-year survival rates exceeding 90% have been reported in isolated cases, and neonates with multiple anomalies generally have 20-30% infant mortality, while 27-38% of the cases with chromosomal defects survive the first year. [5,9,33] Our one-year survival of those with abnormal karyotype was lower than previously reported (17%). On the other hand, cases with multiple anomalies in our cohort had excellent prognosis with only 12% infant mortality. We believe that both numbers may be affected by a relatively small sample size. For unknown reasons, the mortality of isolated cases remains reasonably high, at 20%. However, as all stillbirths have been reported as isolated omphalocele cases, it is possible, that some of the mortalities during the first day of life have also been falsely reported as isolated cases causing bias into the national anomaly register.

In conclusion, omphalocele is associated with high mortality in neonates with abnormal karyotype. However, in the absence of aneuploidy, the survival rates are relatively good even with multiple anomalies. Termination rates remain high due to frequency of associated anomalies. Our study, however, suggests that isolated cases may be more common than previously thought.

The primary limitation is that this study relies on the accuracy of register data. Our study is further limited to relatively small numbers.

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Conflict of Interest

None.

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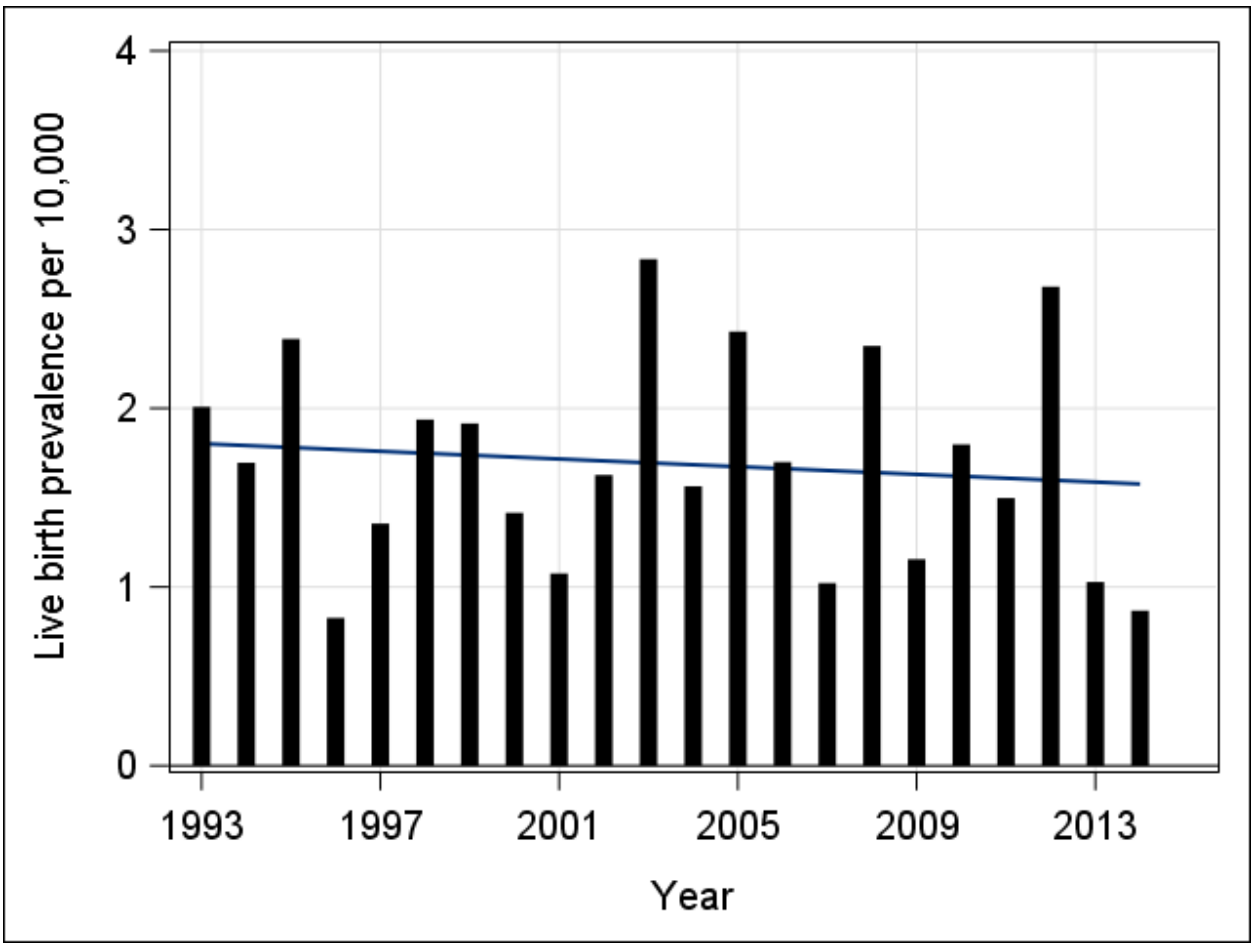

Figure 1. No significant change in the livebirth prevalence in Finland was observed in our study.

Tertiary Center	Number of live born cases	Infant mortality (%)	Abortion rate (%)
Helsinki	72	26.4	68.9
Turku	21	19.1	66.7
Tampere	47	25.5	48.5
Kuopio	40	17.5	51.1
Oulu	33	21.2	53.0

Table 1. Case distribution of omphalocele cases in Finland. No differences were found in survival. However, termination of pregnancy was significantly more common in the south coast of Finland (Helsinki and Turku) compared with the rest of the country (p=0.03).

	Chromosomal	Heart	CNS	Gastrointestinal	Urogenital	Skeletal	BWS	CDH
Born (n=268)	12 (4.5%)	17 (6.3%)	4 (1.5%)	8 (3.0%)	8 (3.0%)	8 (3.0%)	8 (3.0%)	2 (0.7%)
Aborted (n=332)	44 (13%)	4 (1.2%)	14 (4.2%)	4 (1.2%)	4 (1.2%)	4 (1.2%)	-	4 (1.2%)
All (n=600)	56 (9.3%)	21 (6.3%)	18 (3.0%)	12 (2.0%)	12 (2.0%)	12 (2.0%)	8 (1.3%)	6 (1.0%)

Table 2. The most common anomalies associated with omphalocele. BWS: Beckwith-Wiedemann syndrome; CNS: Central nervous system; CDH: Congenital diaphragmatic hernia

	Number of cases	Alive at the age of one (%)	Infant mortality
Isolated omphalocele	176	141	19.9%
Multiple anomalies	41	36	12.2%
Chromosomal abnormalities	12	2	83.3%
Total	229	179	78.2%

Table 3. Survival and infant mortality of omphalocele.

Time period	Number of live born cases	Infant mortality (%)
1995 – 1999	43	34.9
2000 – 2004	54	11.1
2005 – 2009	48	18.8
2010 – 2014	45	17.8

Table 4. A statistically significant decline in mortality rate was observed after the first five years of our study period (p=0.03).