Increasing Risk of Gastroschisis in Norway: An Age-Period-Cohort Analysis

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The prevalence of gastroschisis in Norway, as reported to the Medical Birth Registry of Norway, increased regularly and sixfold from 0.5 to 2.9 per 10,000 births during 1967–1998. The prevalence was also consistently higher among children of younger mothers. The authors used age-period-cohort analysis to assess effects of both parents' age and year of birth (parental cohorts). Mother's and father's age were included in three different regression models. Apart from a significantly higher risk at a young maternal age, the authors also found higher risk at a young paternal age (1.6-fold per 10 years' reduction in father's age, 95% confidence interval: 1.0, 2.4). The time trend was highly significant regardless of whether it was ascribed to period, mother's year of birth, or father's year of birth. However, when father's year of birth was used to describe the time trend, no apparent additional effect of father's age was found, only for mother's age. The time trend is likely caused by environmental factors. Persistently increasing risks among children of young mothers may hypothetically be related to lifestyle factors. A contribution to risk also from fathers born in more recent years or from young fathers increases the likelihood that a factor related to modern lifestyles of young couples may be related to risk.

age factors; gastroschisis; life style; models, statistical; risk factors

Abbreviation: MBRN, Medical Birth Registry of Norway.

Gastroschisis is a birth defect characterized by a fissure of the abdominal wall, exposing the viscera. The defect does not involve the umbilicus. Such defects are considered distinct and are classified as omphalocele.

Many reports exist of a secular increase and of a constant birth prevalence of gastroschisis and omphalocele, respectively, in the Nordic and many other countries (1–12). An increasing trend was reported in Norway as early as 1982 (2). Most of these reports also confirm a higher risk among children of younger mothers. This finding has led to speculations about possible effects of exposures and lifestyle factors that could be more common among younger mothers, including use and abuse of recreational drugs, smoking, dietary and cultural habits, and infections (13–17). However, if the effect of young maternal age reflects the effect of lifestyle-related factors, young paternal age might also be related to the risk. To our knowledge, the possibility of an independent effect also of father’s age has not yet been studied.

Another possible indicator of a couple’s lifestyle could be their years of birth (cohorts of fathers or mothers). Tobacco smoking is one example of a lifestyle factor that has been suggested to follow a pattern determined by a person’s year of birth (18, 19). Smoking appears to be related to the risk of gastroschisis but may hardly explain the time trend (13, 14). Other lifestyle factors such as the tendency to use certain legal and illegal drugs also appear to be associated with gastroschisis (15–17). Lifestyle factors that may have increased and still are increasing in popularity among younger people may follow cohort patterns. If so, and if these factors are important, the level of risk of gastroschisis could be determined more by the parents’ calendar years of birth.
birth (cohort effects) than by year of birth of the child (period effects). A cohort effect could, for example, be detected as
an increase started by a certain birth cohort of parents, a pattern that could provide a basis for constructing new causal
hypotheses.

Under certain conditions, a change in prevalence by time may be ascribed to either period or cohort effects through an
age-period-cohort analysis. Clayton and Shiffers (20, 21) developed a framework for such analyses based on regression
models. This framework may be extended to include the effect of both father’s and mother’s ages and cohort effects
for reproductive outcomes.

In this study, we used data from the Medical Birth Registry of Norway (MBRN) to describe time trends in the preva-
ience of gastroschisis in Norway from 1967 to 1998. This paper describes possible effects of maternal and paternal
ages. Finally, we used logistic regression models in an attempt to ascribe the time trend to either period or cohort
effects. Since important lifestyle factors may be related to maternal as well as paternal cohorts, we expanded the age-
period-cohort analysis to include effects of both maternal age and cohort and paternal age and cohort. Since there is a
potential for misclassification between the categories of gastroschisis and omphalocele, some analyses were also
performed for the category of omphalocele.

MATERIALS AND METHODS

The MBRN is based on a notification system regarding the outcomes of all pregnancies of more than 16 weeks of gesta-
tion that has been compulsory in Norway since 1967 and is based on a one-page form. Between 1967 and 1998, the
MBRN recorded about 1.9 million births (22). Birth defects detected within 1 week of delivery are reported to the MBRN
as written, specific diagnoses. The International Classification of Diseases, Eighth Revision, with some modifications,
has been used to code birth defects. Before 1979, only one code was used to identify abdominal wall defects. At that
point, however, concern for an increasing prevalence of gastroschisis prompted the MBRN to contact all departments
of pediatric surgery in Norway with the request to identify and report in an ad hoc study all cases of gastroschisis and
omphalocele treated since 1967. On the basis of surgical reports, 232 abdominal wall defects were identified—60
with gastroschisis and 172 with omphalocele. At that time, a separate code was established for gastroschisis in the
registry, and the 60 cases were recoded accordingly.

Nevertheless, omphalocele remained in a pooled category with umbilical hernia (International Classification of
Diseases, Eighth Revision, code 555.1) until 1987, when it was given a separate code. In the 1990s, all forms (for 580
births) with this code were recoded on the basis of the verbal description on the original notification form. Altogether, 214
cases were described as omphalocele and were recoded accordingly.

In the MBRN, the mother and father are registered by using national identification numbers that include their dates
of birth. While none of the mothers was missing identification, such information was missing for 130,536 (7.0 percent)
of the fathers.

Maternal and paternal ages were computed as age in days but were scaled to whole years with decimals (including the
second-degree term of maternal age). In some analyses, we categorized maternal and paternal age into 5-year groups, as
shown in table 1. In all models, parental cohorts were measured in single years.

Advances in prenatal diagnostics may affect overall reporting. Children with gastroschisis may benefit from
prenatal detection of the defect and delivery at a highly specialized hospital. In Norway, children with a prenatal
diagnosis of gastroschisis are often delivered at one particular hospital (Trondheim University Hospital). We adjusted
for maternity institution, with Trondheim as one category and all other institutions as the reference category. An
adjustment for maternity institution was incorporated since there may have been different levels of ascertainment at
these categories of institutions. However, geographic analyses of risk were not performed in this study.

Clayton and Shiffers (20, 21) developed a framework for age-period-cohort analyses based on regression models. If
the time trend is a linear drift, it may be described as either a trend by cohort or a trend by period. Because of linear
dependencies between the variables age, period, and cohort, only two of the three linear variables may be used in any
particular model.

Use of age-period-cohort models in our study involved five time-related quantities: mother’s age, mother’s year of
birth (maternal cohort), father’s age, father’s year of birth (paternal cohort), and child’s year of birth (period). Linear
relations between these variables reduce the number of variables that may be used simultaneously in any particular
regression model. In fact, no more than three of the five variables may be entered at a time as linear factors in a regres-
sion model. We decided that the effect of mother’s age and father’s age should be included in all of our analyses. Three
alternative models that included those two age effects could then be fitted to the data: one in which the time trend was
described by the child’s year of birth (period), one in which the time trend was described by the mother’s year of birth
(maternal cohort), and one in which the time trend was described by the father’s year of birth (paternal cohort).

Since our population-based data included children from the same sibships, we also used robust estimation of vari-
ances, confidence limits, and p values to account for correlation between children of the same mother. All analyses were
performed by using the statistics package STATA (23) except the confidence limits for binomial proportions, which were
calculated by using StatXact (24).

RESULTS

Between 1967 and 1998, 291 gastroschisis cases and 408 omphalocele cases were reported in Norway, which gives a
total prevalence at birth of 1.6 and 2.2 (per 10,000 births), respectively, during the same period. A total of 251 (86.3
percent) gastroschisis cases and 279 (68.4 percent) omphalocele cases were livebirths.

However, the prevalence of gastroschisis increased sixfold from 0.5 per 10,000 births in 1967–1974 to 2.9 per 10,000
births in 1995–1998 (p < 0.001) (figure 1) and appears to
continue to increase. In spite of small fluctuations, the prevalence of omphalocele remained relatively stable at about 2.1 per 10,000 births during the same period.

Maternal age was clearly negatively associated with the prevalence of gastroschisis (table 1). Maternal-age-specific prevalences of omphalocele appeared to have a slightly U-shaped distribution, with the lowest risk for children of parents about 30 years of age.

The effects of maternal age on gastroschisis and omphalocele are depicted in figures 2 and 3 according to the mother’s year of birth (maternal cohort) and the child’s year of birth (period). For gastroschisis, we observed a consistent pattern of higher risks for children of mothers less than 20 years of age. A weak tendency toward an increased risk was found for mothers older than age 35 years, but not for all periods or cohorts. For omphalocele, much weaker effects were seen for maternal age, but consistently increased risks were found for higher age.

Both by time period and maternal cohorts, the risks of gastroschisis increased consistently for all maternal age categories (figures 2 and 3). The risk increased from 1.3 per 10,000 in the period before 1975 to 10.2 per 10,000 in the period after 1994 for mothers younger than age 20 years (figure 3). However, because our data indicated that the number of young mothers decreased from 10 percent in the period before 1975 to 3 percent in the period after 1994, fewer mothers were in the high-risk category in more recent years. On the basis of the age category of mothers older than age 35 years (figure 2), it appears that the increase had already started for the cohort of mothers born between 1950 and 1954 since the risk was already increased compared with that for the older cohorts.

The strong parallelism of the age curves by both period and cohort reflects the regularity of the time trend and made it difficult to separate a cohort effect from a period effect. Omphalocele had a slightly different age effect, with clearly increasing rates for higher maternal age. No clear time trend was found for any age group.

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**TABLE 1.** Prevalence* of gastroschisis and omphalocele by mother and father’s age groups, Norway, 1967–1998

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Total births (no.)</th>
<th>Gastrochisis (no. of cases)</th>
<th>Omphalocele (no. of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td></td>
<td>Total cases = 291</td>
<td>Total cases = 408</td>
</tr>
<tr>
<td>&lt;20</td>
<td>129,089</td>
<td>4.88 (63)</td>
<td>2.56 (33)</td>
</tr>
<tr>
<td>20–24</td>
<td>557,466</td>
<td>2.41 (126)</td>
<td>2.26 (126)</td>
</tr>
<tr>
<td>25–29</td>
<td>647,936</td>
<td>1.05 (68)</td>
<td>1.90 (123)</td>
</tr>
<tr>
<td>30–34</td>
<td>373,968</td>
<td>0.67 (23)</td>
<td>1.79 (67)</td>
</tr>
<tr>
<td>35–39</td>
<td>134,138</td>
<td>0.75 (10)</td>
<td>2.98 (40)</td>
</tr>
<tr>
<td>≥40</td>
<td>26,791</td>
<td>0.37 (1)</td>
<td>7.09 (19)</td>
</tr>
<tr>
<td>Father</td>
<td></td>
<td>Total cases = 232†</td>
<td>Total cases = 332‡</td>
</tr>
<tr>
<td>&lt;20</td>
<td>10,386</td>
<td>7.70 (8)</td>
<td>1.93 (2)</td>
</tr>
<tr>
<td>20–24</td>
<td>256,133</td>
<td>2.93 (75)</td>
<td>2.30 (59)</td>
</tr>
<tr>
<td>25–29</td>
<td>587,098</td>
<td>1.53 (90)</td>
<td>2.10 (123)</td>
</tr>
<tr>
<td>30–34</td>
<td>498,559</td>
<td>0.86 (43)</td>
<td>1.62 (81)</td>
</tr>
<tr>
<td>35–39</td>
<td>250,453</td>
<td>0.32 (8)</td>
<td>1.28 (32)</td>
</tr>
<tr>
<td>40–44</td>
<td>94,479</td>
<td>0.74 (7)</td>
<td>2.33 (22)</td>
</tr>
<tr>
<td>45–49</td>
<td>30,785</td>
<td>0.65 (2)</td>
<td>3.25 (10)</td>
</tr>
<tr>
<td>≥50</td>
<td>10,959</td>
<td>2.74 (3)</td>
<td></td>
</tr>
</tbody>
</table>

* Per 10,000 (live- and stillbirths).
† Ages of 59 fathers were missing.
‡ Ages of 76 fathers were missing.

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**FIGURE 1.** Time trend of birth prevalence (including 95% confidence intervals (vertical bars)) of gastroschisis and omphalocele in Norway, 1967–1998.
Paternal and maternal age were highly correlated in our data ($r = 0.76$, 95 percent confidence interval: 0.76, 0.77). Assessment of a possible effect of father’s age in the presence of a maternal age effect therefore requires careful adjustment for maternal age. The crude effect of father’s age is evident in table 1 but may mostly reflect the effect of mother’s age. Mother’s and father’s ages were therefore entered into a logistic regression model as well as time period and place of birth. The independent effect of father’s age was significant ($p = 0.024$) and in the same direction as that of mother’s age (table 2). The estimated effect corresponds to a 1.6-fold increase per 10 years’ reduction in father’s age (95 percent confidence interval: 1.0, 2.4). The time trend by period was highly significant in this model. However, prevalence for the period 1980–1984 was significantly higher than predicted by the trend. A variable accounting for this period was included in all subsequent models.

Alternative models in which the time trend was ascribed to either maternal cohorts or paternal cohorts are shown in tables 3 and 4. When maternal cohort was used to describe the time trend (table 3), the estimated maternal age effect was changed. Similarly, when paternal cohort was used to describe the time trend (table 4), the effect of father’s age was changed and was no longer significant.

**DISCUSSION**

The risk of gastroschisis in Norway has continued to increase dramatically for more than three decades and, during the observation period, showed no signs of leveling off. The prevalence of gastroschisis was estimated as 2.9 per 10,000 in the most recent years in Norway (figure 1). Only a couple of higher prevalences have been reported: 4.9 per 10,000 in Mexico (12) and 4.4 per 10,000 in southwest England (6). The time trend of increasing prevalence was also recently confirmed in Australia, Finland, France, Ireland, Japan, Mexico, and South America (12).

The maternal age effect described in other studies (1–12) was also present in our data. Furthermore, the effect during the observation period, showed no signs of leveling off. The prevalence of gastroschisis was estimated as 2.9 per 10,000 in the most recent years in Norway (figure 1). Only a couple of higher prevalences have been reported: 4.9 per 10,000 in Mexico (12) and 4.4 per 10,000 in southwest England (6). The time trend of increasing prevalence was also recently confirmed in Australia, Finland, France, Ireland, Japan, Mexico, and South America (12).

The maternal age effect described in other studies (1–12) was also present in our data. Furthermore, the effect

![FIGURE 2. Birth prevalence of gastroschisis and omphalocele by maternal age and mother's year of birth (maternal cohorts), Norway, 1967–1998.](image1)

![FIGURE 3. Birth prevalence of gastroschisis and omphalocele by maternal age and child's year of birth (periods), Norway, 1967–1998.](image2)

**TABLE 2. Logistic regression analysis of the effects of mother's and father's age and time period on risk of gastroschisis, Norway, 1967–1998**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio*</th>
<th>95% CI†</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>-0.58</td>
<td>-0.78, 0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maternal age squared</td>
<td>0.01</td>
<td>0.00, 0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Father’s age (per year)</td>
<td>0.95</td>
<td>0.91, 0.99</td>
<td>0.024</td>
</tr>
<tr>
<td>Period trend (per year)</td>
<td>1.09</td>
<td>1.07, 1.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Period 1980–1984</td>
<td>1.65</td>
<td>1.13, 2.41</td>
<td>0.009</td>
</tr>
</tbody>
</table>

* Also adjusted for categories of maternity institutions.
† The confidence interval (CI) and p value were based on robust estimation of variances by accounting for correlation between children from the same sibship.
‡ Log odds ratios (βs) from the model. These parameters must be combined to obtain the odds ratios between specific ages.
appeared to be relatively consistent over time. In addition, we found an independent effect of father’s age, a phenomenon that, to our knowledge, has not been reported before. The effect was weaker than the effect of mother’s age but was in the same direction, with higher risks when the father was young. The strong correlation between mother’s and father’s ages created a risk of residual confounding from mother’s age. However, our careful adjustment for mother’s age using regression models with both first- and second-order terms should have reduced the chances of residual confounding to a minimum. A contribution of young age of both parents to higher risks should be expected if a component of modern lifestyles of younger couples was responsible for the gastroschisis epidemic, irrespective of the biologic mechanism involved. Paternal involvement does not necessarily mean that a particular factor is transmitted from the father at conception.

The time trend of gastroschisis was almost linear and appeared to be consistent for all maternal age categories. The regularity of this pattern implies that whatever factors have contributed to the increase in risk increased gradually in all age categories and began with the first calendar years we observed in our study; that is, the increase had apparently already started for all age groups at the beginning of our observation period more than 30 years ago (figure 2). Therefore, the increase is probably not attributable to a factor introduced more recently.

Mother’s age and time trend were highly significant factors in all regression models (tables 2, 3, and 4). However, father’s age was not significant when time trend was described as an effect of cohorts of fathers (table 4). The effect of father’s age was a reduction in the risk by increasing age. The general time trend was in the other direction: an increase by increasing calendar year. Apparently, the increasing prevalence of gastroschisis by father’s year of birth compensated for and removed the expected reduction in risk by age. An effect of father’s age or of father’s cohort may therefore be alternative expressions of a paternal contribution to the risk of gastroschisis. At least one of them is necessary for a proper description of variation by age and time.

The model described in table 4, in which time trend is described by father’s cohort, is more parsimonious than the models described in tables 2 and 3. Therefore, one could also speculate that the component of a couple’s lifestyle related to the risk of gastroschisis correlates better to the father’s year of birth than to the mother’s or child’s year of birth.

Examples of lifestyle-related factors have been discussed previously (13, 14, 16). In California, use of recreational drugs by both parents during pregnancy was associated with gastroschisis, while an association with use by the father was implicated (16). In our study, we cannot rule out the effect of such modern lifestyle behaviors that have increased in popularity, especially among young couples.

Cohort effects for gastroschisis were previously implicated in a study from Sweden (25). Despite the intriguing simplicity of the model that described time trend by father’s cohort (table 4), we would not interpret our study as evidence of particular cohort effects or a clear demonstration that the risk of gastroschisis was determined more by cohort than by period.

Problems of misclassification between gastroschisis and omphalocele and underreporting of abdominal wall defects have been raised as serious concerns (26, 27). Data on gastroschisis and omphalocele from the MBRN, similar to other population-based registries, are likely to reflect such problems. We could not directly assess the degree of misclassification between these two related abdominal wall defects. A misclassification occurring in the clinic is likely to also be included in the MBRN. However, when diagnoses were too unspecific, for example, in reporting an abdominal wall defect only, the MBRN contacted the clinic to obtain a more specific diagnosis.

The completeness of ascertainment of gastroschisis and omphalocele is not known. For two more common, serious external birth defects—neural tube defects and cleft lip—the proportions of cases ascertained by the registry have been estimated as approximately 90 percent and 80 percent, respectively (28). Special efforts by the MBRN to ascertain...
abdominal wall defects in 1979 and the early 1980s may have resulted in the rates for this period (1980–1984) being higher than those predicted by the regular trend. A review of all records on gastroschisis and omphalocele and regular communication with maternity institutions and surgical departments may have increased awareness and ascertainment during this period. However, it is most unlikely that the whole trend is due to such improved ascertainment. The rate of gastroschisis has increased twofold since 1980–1984, and no similar trend has been observed for omphalocele. The fact that the risks of omphalocele remained almost unchanged also reduces the likelihood that the increase in gastroschisis was caused by misclassification within the category of abdominal wall defects.

In conclusion, the risk of gastroschisis appears to have increased throughout the observation period of this study. Young maternal age remained a strong risk factor. Young paternal age or a recent paternal year of birth was also a risk factor. Despite the limitations of ascertainment problems for abdominal wall defects, this pattern of risks seems compatible with the existence of unknown risk factors related to the lifestyles of younger couples.

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REFERENCES