Pre- and Perinatal Risk Factors for Pyloric Stenosis and Their Influence on the Male Predominance

Camilla Krogh*, Sanne Gørtz, Jan Wohlfahrt, Robert J. Biggar, Mads Melbye, and Thea K. Fischer

* Correspondence to Dr. Camilla Krogh, Department of Epidemiology Research, Statens Serum Institut, 5 Orestads Boulevard, DK-2300 Copenhagen S, Denmark (e-mail: ckr@ssi.dk).

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Pyloric stenosis occurs with a nearly 5-fold male predominance. To what extent this is due to environmental factors is unknown. In a cohort of all children born in Denmark, 1977–2008, the authors examined the association between pre- and perinatal exposures and pyloric stenosis and investigated whether these factors modified the male predominance. Information on pre- and perinatal factors and pyloric stenosis was obtained from national registers. Poisson regression models were used to estimate rate ratios. Among 1,925,313 children, 3,174 had surgery for pyloric stenosis. The authors found pyloric stenosis to be significantly associated with male sex, age between 2 and 7 weeks, early study period, being first born, maternal smoking during pregnancy, preterm delivery, small weight for gestational age, cesarean section, and congenital malformations. Among cases, 2,595 were males and 579 were females. Lower male predominance was associated with age at diagnosis outside the peak ages, early study period, no maternal smoking during pregnancy, preterm delivery, and congenital malformations. The authors have previously found a strong familial aggregation of pyloric stenosis indicating a genetic influence. This study shows that environmental factors during and shortly after pregnancy also play a role and that several of these modify the strong male predominance.

Abbreviations: CI, confidence interval; ICD, International Classification of Diseases.

Pyloric stenosis, also known as infantile hypertrophic pyloric stenosis, is the most common condition requiring surgery in the first months of life (1). It is characterized by a marked hypertrophy of the pylorus muscle, which leads to a blockage of the gastric outlet and provokes increasingly severe episodes of projectile vomiting. In Ramstedt pyloromyotomy, the circular muscle is incised longitudinally without closure, which relieves the obstruction permanently (2). The incidence of pyloric stenosis in Denmark is 1–2 per 1,000 livebirths, and nearly all pyloric stenosis cases in Denmark are believed to be treated with surgery (3, 4).

Although treatment is well established for pyloric stenosis, the etiology of this condition is still an enigma. The risk of pyloric stenosis is nearly 5 times more common in male than female infants (3, 5–8). The explanation for this skewed sex distribution remains unclear. The sharp changes in incidence argue strongly in favor of modifiable environmental influences on the risk of pyloric stenosis (9). However, familial clustering (3, 10) also suggests a role for genetics. Whether the strong male predominance is mediated through interactions with the environment or has a male-specific genetic component is unknown. We decided to address this question by investigating whether pre- and perinatal environmental factors that might be associated with pyloric stenosis development modified the male predominance of the disease.

In the present study, we took advantage of the unique Danish population-based registries to examine pre- and perinatal risk factors for pyloric stenosis and furthermore to investigate whether such factors modified the male predominance.

MATERIALS AND METHODS

Study cohort

The study was based on a large cohort including all children born in Denmark between 1977 and the end of 2008. The
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A cohort was identified by means of the Danish Civil Registration System. Since April 1968, the Danish Civil Registration System has registered sex, date and place of birth, identity of parents, and updated information on vital status and emigration, by using a unique personal identification number assigned to each Danish resident (11). This number permits accurate linkage of individual-level information among other nationwide registers in Denmark.

Exposures

Information on the infant’s sex, date and place of birth, and birth order was obtained from the Danish Civil Registration System. Data on maternal age at birth, gestational age, birth weight, maternal smoking during pregnancy, and cesarean section were based on information from the Danish Medical Birth Registry (12). From 1997 and onward, we had information on whether the cesarean section was elective or acute. Weight for gestational age was calculated by using the observed birth weight distribution within strata of sex and gestational age in the cohort. Time since conception was calculated by using gestational age. Information on congenital malformations and hospital admissions during follow-up was obtained from the Danish National Patient Register (13). Congenital malformations were defined by using the EUROCAT definition according to International Classification of Diseases (ICD), Tenth Revision, codes Q00–Q99, D215, D821, D1810, P350, P351, and P371, excluding the minor malformations. Information on congenital malformations was not available until 1994.

Outcome

Information on pyloric stenosis was obtained by linkage with the Danish National Patient Register. This register contains a nationwide registration of all somatic hospital discharge diagnoses and operations performed since 1977 (13). Pyloric stenosis cases were defined as children who in their first year of life had a pyloromyotomy according to the Danish Classification of Surgical Procedures codes up to December 1995 (ICD, Eighth Revision, codes 41840, 41841, and 44100) (14) and, from January 1996, the Nordic Classification of Surgical Procedures codes (ICD, Tenth Revision, codes KJDH60 and KJDH61) (15).

Statistical analyses

The association between pre- and perinatal factors and the risk of pyloric stenosis was evaluated by (incidence) rate ratios estimated in a Poisson regression model using the procedure GENMOD in SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina). Male predominance was evaluated by the male/female ratio. The male/female ratios were estimated in the same framework as the rate ratio of pyloric stenosis in males versus females according to the pre- and perinatal factors by including an interaction term between sex and the pre- and perinatal factors, that is, investigating how these factors modify the male/female ratio. Infants were followed from birth until 1 year, death, emigration, designation “missing person” in the Danish Civil Registration System, pyloric stenosis diagnosis, or December 31, 2008, whichever occurred first. Adjustment variables were chosen a priori on the basis of the literature and biologic considerations, and no subsequent model reduction was performed. As a crude reflection of the potential causal mechanisms, variables were divided into 3 groups: 1) basic variables (age, period, and sex); 2) maternal characteristics before pregnancy (birth order and maternal age); and 3) pre- and perinatal factors. In the main analyses, variables in group 1 were adjusted for the other factors in group 1, and variables in groups 2 and 3 were adjusted for variables in groups 1 and 2; that is, rate ratios for sex, age, and period were adjusted for each other, and all other rate ratios were adjusted for sex, age (0–1, 2, 3, 4, 5, 6, 7, 8–9, 10–11, 12–13, 14–16 complete weeks), period (years 1977–1981, 1982–1986, 1987–1991, 1992–1996, 1997–2001, 2002–2008), birth order (first, second, third, and later), and maternal age at birth (<20, 20–25, 25–<30, 30–<35, 35–<40, ≥40 years). When defining age into finer categories (4-day intervals), we observed similar main effects. Male/female ratios were adjusted for the same variables as the rate ratios but with the extension that the sex-specific effects of the adjustment variables were used, that is, introducing interaction terms between sex and the adjustment variables in the Poisson regression model.

In additional analyses, we furthermore adjusted for selected potential intermediate variables (e.g., adjusting gestational age for cesarean section). In order to elucidate the etiologic pathway between exposure and pyloric stenosis, we based these additional analyses on the assumption of no uncontrolled common cause of the intermediate variable and pyloric stenosis (16). Age, time since conception, period, congenital malformations, and being at hospital a week earlier were treated as time-dependent variables. Congenital malformation was defined as current history of congenital malformations in order to avoid possible surveillance bias. We chose to ascribe hospital admission status during follow-up as being hospitalized 1 week earlier to exclude hospitalizations caused by symptoms basically reflecting an underlying pyloric stenosis. The presented P values for homogeneity of rate ratios represent tests for main effects, and P values for homogeneity of male/female ratios represent tests for interactions. All tests were 2-sided likelihood ratio tests. Estimates were presented for missing categories, but when tests and adjustments were performed, the missing categories were excluded. Deviance was used to compare model fit when using time since conception instead of age in an additional analysis.

RESULTS

Pre- and perinatal risk factors

Among 1,925,313 singleton infants, 3,174 infants had surgery for pyloric stenosis. Table 1 shows rate ratios of pyloric stenosis according to sex, age, and period. Among cases, 2,595 (81.8%) were male infants, and 579 (18.2%) were female infants, resulting in a 4.48/1 male/female ratio, which was reduced to 4.26 (95% confidence interval (CI): 3.89, 4.66) after taking person-years into account and adjusting for age and period. The cumulative risk at 1 year for male and female infants was 0.27% and 0.06%, respectively. The rate of pyloric stenosis peaked at age 2–7 weeks (Table 1).
The mean age at diagnosis was 38 days; 95% of the cases were diagnosed between age 2 and 11 weeks. The median age at diagnosis was 34 days, with 25% diagnosed within 26 days and 75% within 46 days. Only 31 infants were diagnosed in the first week.

The overall incidence of pyloric stenosis decreased significantly between 1977 and 2008 ($P < 0.0001$), the most pronounced decrease being in the early 1990s (Table 1). Adjusting period for birth order, maternal age, maternal smoking during pregnancy, gestational age, weight for gestational age, cesarean section, and congenital malformations did not change the decrease in incidence (results not shown).

Table 2 shows rate ratios of pyloric stenosis according to birth order, maternal age, and maternal smoking during pregnancy. The rate ratio of pyloric stenosis was highest in first-born infants compared with later-born infants. Thus, compared with first-born infants, second-born and later-born infants had rate ratios of 0.69 (95% CI: 0.64, 0.75) and 0.67 (95% CI: 0.60, 0.75), respectively. The rate ratios were similar after adjustment for cesarean section. We found no significant association between maternal age and the risk of pyloric stenosis after adjusting for birth order ($P = 0.81$). The rate of pyloric stenosis was 63% (95% CI: 43, 85) higher in infants of smoking mothers than among infants of nonsmoking mothers. Rate ratios for all other factors examined were nearly similar with and without adjustment for maternal smoking during pregnancy (results not shown).

Table 3 shows rate ratios of pyloric stenosis according to gestational age, weight for gestational age, cesarean section, and congenital malformations. Overall, the mean gestational age was 39 weeks for both infants with and without pyloric stenosis. However, infants who were born at an early gestational age had a higher rate of pyloric stenosis compared with infants born later ($P < 0.0001$). Thus, compared with mature infants ($\geq 37$ weeks), premature infants ($< 37$ weeks) had an 84% (95% CI: 61, 110) higher rate of pyloric stenosis. The higher rate was also observed after additional adjustment for cesarean section (rate ratio of 66%, 95% CI: 45, 90). To evaluate whether the higher rate is due to the higher level of hospitalization in early born children, we performed an

| Table 1. Rate Ratios of Pyloric Stenosis According to Sex, Age, and Period in All Children Born in Denmark, 1977–2008 |
|---------------------------------|-----------------|----------------|----------|-----------------|---------|
| Sex                             | Person-Years    | Cases, no.     | Adjusted RR$^a$ | 95% CI          | Adjusted M/F Ratio$^b$ | 95% CI |
|---------------------------------|-----------------|----------------|----------|-----------------|---------|
| Males                           | 964,847         | 2,595          | 4.26     | 3.89, 4.66      | <0.0001 |
| Females                         | 917,343         | 579            | 1        | Referent        |         |
| $P$ value$^c$                   |                 |                |          |                 |         |
| Age, weeks                      |                 |                |          |                 |         |
| 0–1                             | 37,478          | 35,540         | 69       | 22              | 0.18    | 0.14, 0.23 | 3.59    | 2.12, 6.29 |
| 2                               | 18,707          | 17,745         | 238      | 39              | 1.13    | 0.95, 1.34 | 6.99    | 4.64, 10.8 |
| 3                               | 18,685          | 17,730         | 500      | 95              | 2.42    | 2.09, 2.82 | 6.03    | 4.35, 8.48 |
| 4                               | 18,661          | 17,716         | 562      | 130             | 2.82    | 2.44, 3.27 | 4.95    | 3.64, 6.84 |
| 5                               | 18,637          | 17,701         | 420      | 84              | 2.06    | 1.77, 2.40 | 5.73    | 4.10, 8.15 |
| 6                               | 19,595          | 18,617         | 285      | 65              | 1.36    | 1.16, 1.60 | 5.03    | 3.51, 7.33 |
| 7                               | 19,595          | 18,617         | 201      | 43              | 1      | Referent    | 5.36    | 3.58, 8.21 |
| 8–9                             | 37,137          | 35,304         | 194      | 53              | 0.51    | 0.42, 0.61 | 4.20    | 2.86, 6.29 |
| 10–11                           | 37,077          | 35,252         | 65       | 20              | 0.17    | 0.14, 0.22 | 3.73    | 2.17, 6.68 |
| 12–13                           | 37,990          | 36,124         | 27       | 16              | 0.09    | 0.06, 0.12 | 1.94    | 1.01, 3.85 |
| $\geq$14                       | 702,286         | 667,942        | 34       | 12              | 0.01    | 0.00, 0.01 | 3.26    | 1.65, 6.83 |
| $P$ value$^c$                   |                 |                |          |                 | <0.0001 |
| Period, years                   |                 |                |          |                 | 0.02    |
| 1977–1981                       | 133,068         | 126,838        | 536      | 115             | 2.44    | 2.16, 2.76 | 4.63    | 3.21, 6.81 |
| 1982–1986                       | 130,326         | 124,609        | 556      | 149             | 2.89    | 2.56, 3.27 | 3.71    | 2.60, 5.41 |
| 1992–1996                       | 167,984         | 159,337        | 314      | 72              | 1.23    | 1.07, 1.42 | 4.32    | 2.90, 6.56 |
| 1997–2001                       | 163,960         | 155,804        | 233      | 34              | 0.88    | 0.75, 1.02 | 6.80    | 4.27, 11.2 |
| 2002–2008                       | 220,364         | 209,678        | 346      | 64              | 1      | Referent    | 5.36    | 3.58, 8.21 |
| $P$ value$^c$                   |                 |                |          |                 | <0.0001 |
| Abbreviations: CI, confidence interval; M/F, male/female; RR, rate ratio. |
| $^a$ Adjusted for sex, age, and period. |
| $^b$ Adjusted for the sex-specific effects of age and period. |
| $^c$ $P$ values refer to tests for homogeneity. |

additional adjustment for being hospitalized a week earlier and observed the same high rate after adjustment for this intermediate variable (rate ratio \(= 96\%, 95\% \text{ CI}: 70, 124\)).

With adjustment for time since conception instead of age in the analysis of gestational age in Table 3, the fit of the model became substantially poorer. Furthermore, the effect of gestational age was still significant.

Infants who were born with small weight for gestational age had a significantly higher rate of pyloric stenosis compared with heavier infants (Table 3).

Infants delivered by cesarean section had a subsequent 61\% (95\% CI: 47, 77) higher rate of pyloric stenosis than infants delivered vaginally. We found no significant difference between acute (rate ratio = 1.40, 95\% CI: 1.13, 1.72) and elective (rate ratio = 1.49, 95\% CI: 1.11, 1.95) cesarean section (\(P = 0.72\)). Infants with congenital malformations had a significantly higher rate of pyloric stenosis with a rate ratio of 1.92 (95\% CI: 0.86, 4.57).

### Male/female ratio by pre- and perinatal risk factors

The sex ratio was modified by many of the pre- and perinatal risk factors examined. The sex ratio varied significantly with age, with the lowest male predominance among the infants diagnosed with pyloric stenosis at the youngest and oldest ages (\(P = 0.02\)) (Table 1). The male predominance (male/female ratio) significantly increased during the study period (\(P = 0.03\)) (Table 1).

The male predominance was borderline significantly higher among infants born to a mother who smoked during pregnancy (male/female ratio = 6.43, 95\% CI: 3.84, 11.0) compared with infants of nonsmoking mothers (male/female ratio = 4.51, 95\% CI: 2.92, 11.4) (\(P = 0.05\)) (Table 2). We also found gestational age to significantly modify the male predominance (\(P = 0.02\)). For both the extremely premature (<28 weeks) and the very premature (28–31 weeks) infants, the risk of pyloric stenosis was nearly similar for male and female infants, with a male/female ratio of about 1.50. For premature infants between 32 and 36 weeks of gestation, the male/female ratio was 3.70 and, for the mature infants, the male/female ratio was about 5 (Table 3). Figure 1 illustrates that the lowered male/female ratio in premature infants is due to a similar rate of pyloric stenosis for premature male and female infants and a lower rate of pyloric stenosis in mature female infants compared with male infants.

The male predominance was significantly lower in infants with congenital malformation (male/female ratio = 1.92, 95\% CI: 0.86, 4.57) compared with infants without (male/
female ratio = 5.11, 95% CI: 3.32, 8.03) (P = 0.02). For birth order (P = 0.18), maternal age (P = 0.21), small weight for gestational age (P = 0.61), and cesarean section (P = 0.15), we did not observe any modification of the male/female ratio for pyloric stenosis.

**DISCUSSION**

In this large, population-based, cohort study of nearly 2 million children, we found the risk of pyloric stenosis to be associated with male sex, age between 2 and 7 weeks, early study period, being first-born, maternal smoking during pregnancy, preterm delivery, small weight for gestational age, cesarean section, and congenital malformation. The sex ratio was modified by many of these pre- and perinatal risk factors. Specifically, the male predominance was lower for infants diagnosed outside the peak age period, for infants born in the early part of the study period, for premature infants, for infants with congenital malformations, and, marginally significantly, for infants of nonsmoking mothers.

**Pre- and perinatal risk factors**

Consistent with our results, those of most studies (7, 17–22), although not all (23–25), have observed first-born infants to
have an overall higher risk of pyloric stenosis. Similarly, offspring of young mothers have been reported to have a higher risk of pyloric stenosis (7, 9, 24, 26). However, in 2 studies, this was not apparent after stratification by birth order (18, 20). In our larger population-based study, we could likewise not document any association between maternal age and the risk of pyloric stenosis after adjusting for birth order. The effect of birth order could not be explained by the effect of cesarean section. Thus, the association with birth order probably reflects the importance of other factors in the neonatal environment. For example, differences in the hormonal or nutritional milieu between first-born and later-born infants may be relevant. Birth order is often used as a proxy for early infections. However, because later-born children are generally more exposed to infections than first-born children, the present study would argue against infections being a risk factor for pyloric stenosis.

Sørensen et al. (27) documented a 2-fold increased risk of pyloric stenosis for infants of smoking mothers. We observed an increased risk of pyloric stenosis (1.6-fold) if the mother smoked during pregnancy. One possible explanation for the association could be that smoking may cause infantile pylorospasm and thereby contribute to hypertrophy of the pylorus muscle, but we have no further data to substantiate this argument.

We documented that premature infants have a nearly 2-fold increased risk of pyloric stenosis compared with mature and postmature infants. Two previous studies investigated the mean gestational age and found no difference in cases and controls (7, 24). However, we likewise found no difference in mean gestational age in infants with and without pyloric stenosis, which reflects that comparing mean gestational age is not the ideal approach to capture increased risk in infants with extreme gestational ages. The effect of prematurity could not be ascribed to differences in birth order or maternal smoking during pregnancy and was apparently not mediated by the effect of cesarean section or subsequent more intensive hospitalization. Furthermore, it has been suggested that the development of pyloric stenosis requires a certain degree of maturation and that the onset of symptoms is rather related to maturity as dated from conception than from birth (7, 18, 24). Schechter et al. (7) indicated that the diagnosis was approximately 1 week later for each earlier week of gestation at birth. However, this explanation of the effect of gestational age is not supported by our data, as the rate of pyloric stenosis was much better described by current age and gestational age than by time since conception and gestational age.

Infants delivered by cesarean section had a higher risk of pyloric stenosis. It is well established that delivery by elective cesarean section is less stressful for the fetus than normal vaginal delivery (28). It is unknown whether reduced stress hormone levels in infants measured after elective cesarean section have a beneficial or a deleterious impact on the infant.

We observed a markedly increased risk of pyloric stenosis among infants with congenital malformations, which has also been documented previously (7, 22). This association might be a result of shared causes.

In line with our results, those of others show a decreasing incidence of pyloric stenosis in Denmark (4, 27), starting in the early 1990s and leveling off during the late 1990s. We speculated that this decreasing incidence to a certain extent could be a result of changing cofactors, such as, for example, the decreasing smoking incidence (29) or the increased mean maternal age (9). However, the declining incidence remained after adjusting for all risk factors examined in this study, and these variables therefore seem insufficient to explain the decreasing incidence of pyloric stenosis. Instead, the reason for the incidence decrease may well be found in the early postnatal environment. Many of the risk factors examined above may be explained by their effect on feeding practice. However, in a subset of the cohort where information on feeding practice was available, the effect of pre- and perinatal factors was not influenced by adjustment for bottle feeding (unpublished data).

**Male/female ratio by pre- and perinatal risk factors**

The elevated male/female risk ratio of 4.26 observed in our study is consistent with previous findings (3, 5–7, 10, 22, 30, 31). The higher risk of pyloric stenosis in males is, however, not well understood. Some studies have speculated that the sex difference might be due to genetics (6, 9, 10, 32–36). However, there is no evidence as yet for a sex-related heritability of pyloric stenosis. Two studies reported the changing incidence pattern to be similar for male and female infants (18, 35), while 2 other studies found the sex ratio to be modified by the calendar year (21, 31). Both latter studies observed a higher male predominance late in the study period. This is consistent with our observation of a lower male predominance in the early part of the study period and indicates the presence of environmental factors acting on the susceptible sex. Male predominance is also a characteristic of other gastrointestinal diseases, such as Hirschsprung (37), intussusceptions (38), and rotavirus gastrointestinal infections (39), and suggests that males might be more susceptible with respect to the development, maturation, and function of the gastrointestinal tract.
Probably the most interesting finding regarding the effect of sex was our documentation of a male/female ratio among premature infants being close to 1. For the mature infants, the majority group, male predominance was the well-known 5-fold. To our knowledge, only 2 studies have investigated the modification of male/female ratio according to gestational age and, consistent with our results, they found a lower male predominance in premature infants (25, 40). This pronounced difference in the male/female ratio between premature and mature infants is an enigma.

We also observed differences in the sex ratio according to age, maternal smoking during pregnancy, and congenital malformation. Female infants were more likely to be diagnosed either particularly early or particularly late, outside the remarkably brief age range of vulnerability that is a defining characteristic of pyloric stenosis. These cases could represent special situations and be the results of other more rare causes. Our finding of a lower male predominance among infants with coexisting malformations is consistent with that from a previous study (22), but the reason for this is unknown.

Strengths and limitations

Major strengths of this study include its design, size, and utilization of unique Danish national registers. The study was conducted as a register-based study in a cohort comprising all children born in Denmark between 1977 and the end of 2008. Furthermore, follow-up was done using up-to-date vital status information from the Danish Civil Registration System, making selection bias and loss to follow-up unlikely.

Information on pre- and perinatal variables was mostly based on the Danish Medical Birth Registry. Validation of this registry has demonstrated good agreement between medical records and the Danish Medical Birth Registry except for a small underestimation of preterm deliveries (41). Exposure information was ascertained before pyloric stenosis onset, making possible misclassification nondifferential. Pyloric stenosis diagnoses were obtained from the Danish National Patient Register in which hospital discharge diagnoses are mandatory and recorded for the entire country. In particular, surgical diagnoses should be considered both accurate and well recorded (42). Pyloric stenosis is a life-threatening condition if the child is not treated, which makes it unlikely that some cases escaped attention. Thus, misclassification of the pre- and perinatal factors and the diagnosis of pyloric stenosis are not likely to explain the observed associations.

In conclusion, we found the risk of pyloric stenosis to be significantly associated with many pre- and perinatal factors, arguing for important environmental factors being involved in the etiology of this condition. Several of the documented risk factors modified the strong male predominance.

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Author affiliations: Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark (Camilla Krogh, Sanne Gørtz, Jan Wohlfahrt, Robert J. Biggar, Mads Melbye, Thea K. Fischer); and The Danish National Board of Health, Copenhagen, Denmark (Thea K. Fischer).

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