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ORIGINAL RESEARCH ARTICLE

Sex of the first-born and obstetric complications in the subsequent birth. A study of 2.3 million second births from Denmark, Finland, Norway, and Sweden

Laust H. Mortensen[1] | Sven Cnattingius[2] | Mika Gissler[3,4] | Kari Klungsøyr[5,6] | Rolv Skjærven[6,7] | Anne-Marie Nybo Andersen[1] | Henriette S. Nielsen[8,9]

[1]Section of Epidemiology, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

[2]Division of Clinical Epidemiology, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

[3]Finnish Institute for Health and Welfare, Helsinki, Finland

[4]Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden

[5]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

[6]Division for Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway

[7]Center for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway

[8]Department of Obstetric and Gynecology, Hvidovre Hospital, University Hospital Copenhagen, Copenhagen, Denmark

[9]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence
Henriette Svarre Nielsen, Department of Obstetric and Gynecology, Hvidovre Hospital, Kettegård Alle 30, 2650 Hvidovre, Denmark.
Email: Henriette.Svarre.Nielsen@regionh.dk

Abstract

Introduction: Studies have shown associations between a first-born boy and increased risks of pregnancy loss, stillbirth, decreased birthweight, and preterm birth in subsequent pregnancies, but with limited precision.

Material and Methods: We examined associations between sex of the first-born and obstetric complications in second births. We calculated the relative risks (RR)s of preeclampsia/eclampsia, placental abruption, stillbirth, and preterm birth in approximately 2.3 million second births comparing women with a preceding first-born boy to those with a first-born girl using the Medical Birth Registries of Denmark, Finland, Norway, and Sweden 1980-2008.

Results: In second births following a first-born boy rather than a girl, the RR was 4% higher for preeclampsia/eclampsia (RR = 1.04, 95% CI 1.02-1.06), 9% higher for placental abruption (RR = 1.09, 95% CI 1.05-1.13), 9% higher for stillbirth (RR = 1.09, 95% CI 1.04-1.14), and 8% higher for preterm birth (RR = 1.08, 95% CI 1.07-1.09). The population attributable risks ranged from 2% to 4.5%.

Conclusions: Male sex of the first-born is associated with small increases in risks of obstetric complications in the second birth. Exploration of the underlying mechanisms is needed to increase our knowledge and treatment options for these serious obstetric complications.

KEYWORDS

offspring sex, placental abruption, preeclampsia/eclampsia, preterm birth, stillbirth

1 | INTRODUCTION

Sex of the first-born infant has been associated with adverse outcomes in subsequent pregnancies. In Denmark a male first-born has been associated with later increased risks of recurrent pregnancy loss, stillbirth, and reduced birthweight.[1-4] In addition, a first male offspring has been associated with later risks of preterm birth in studies based on Danish, Swedish, and Californian medical birth records.[1,5] Among younger brothers, the presence of an older brother has been associated with subtle differences in anthropometrics in young adulthood, which may be indicative of an enduring influence.[6] The exposure is not preventable and the findings are therefore of limited interest in public health. However, these small but consistent findings across populations

Abbreviations: H-Y antigens, male-specific histocompatibility antigens; RR, relative risk.

and complications could be driven by important biological mechanisms that are worth exploring to understand and reveal treatment targets. There are two important limitations of previous studies. First, because the effects are very small, the precision is limited. Second, the existing studies have suggested that using a limited number of variables is feasible because there is little evidence to suggest confounding, but have not been able to systematically assess less common obstetric complications in relation to sex of the first-born because of limited power. By focusing on the obstetric complications in second births using aggregated data from four countries, we seek to amend this.

The aim of this study is to examine the association between sex of the first-born infant in relation to risks of preeclampsia/eclampsia, placental abruption, stillbirth, and preterm birth in the subsequent birth in a sample of approximately 2.3 million second births from the Medical Birth Registries of Denmark, Finland, Norway, and Sweden 1980-2008.

Key message

Having an older brother is associated with a small but consistent increase in preeclampsia, placental abruption, stillbirth, and preterm birth among second-borns. Mechanistic understanding is a first step to specifically address and decrease these complications.

2 | MATERIAL AND METHODS

Information on singleton second births was extracted from the Nordic Birth Registries based on a preceding singleton birth with known sex in the National Medical Birth Registers of Denmark, Norway, Sweden (1980-2008) and Finland (1987-2008). The only restriction applied to the first birth was that the sex of the infant was known. For the second birth we included information for all births from 22 completed gestational weeks on preeclampsia/eclampsia and placental abruption. Analyses of preterm birth were restricted to live births at 22 weeks or later and preterm birth was defined as delivery before 37 completed weeks of gestation. Stillbirth was defined as a fetal death at 28 completed weeks or more, because information on stillbirths before 28 weeks was unavailable in two of the birth registries (Denmark and Sweden). Preeclampsia/eclampsia and placental abruption were defined using standard definitions based on the International Classification of Diseases, 8th to 10th revisions augmented according to national registration procedures. Details of the outcome variables are available in Table 1.

2.1 | Statistical analyses

The risk of each of the outcomes per thousand births was calculated according to sex of the child of the preceding births. The numerator was all cases, and the denominator was all births at risk of becoming cases. Risk differences and relative risks were calculated for each of the countries. The overall estimate was calculated as an inverse variance weighted average. The test of heterogeneity based on

TABLE 1 Outcome variable according to national coding strategies

	DK	FI	NO	SE
Coding of outcomes over time	ICD-8: 1980-1994 ICD-10: 1995-	ICD-9: 1987-30/9/1990 Checkbox: 1/10/1990-2003 ICD-10: 2004-	Adapted ICD-8: 1980-1998 ICD-10: 1999-	ICD-8: 1980-1986 ICD-9: 1987-1996 ICD-10: 1997-
Gestational age	LMP/ultrasound	LMP/ultrasound	LMP	LMP/ultrasound
Stillbirth	GA ≥ 28 completed weeks	GA ≥ 28 completed weeks	GA ≥ 28 completed weeks	GA ≥ 28 completed weeks
Placental abruption	ICD-8: 632.1, 651.4 ICD-10: O45	ICD-9: 641.2 Checkbox: ICD-10: O45	Adapted ICD-8: 632.1, 651.4 ICD-10: O45	ICD-8: 632.1, 651.4 ICD-9: 641.2 (SE: 642C) ICD-10: O45
Eclampsia and preeclampsia including HELLP & preeclampsia superimposed on essential hypertension	ICD-8: 637.19, 637.99, 762.29, 762.39, 762.99 ICD-10: O15 ICD-8: 637.03, 637.04 +SE: 637.10 +DK: 661.3, 762.19, 637.19, 637.99, ICD-10: O11, O14	ICD-9: 637.19, 637.99, 762.29, 762.39, 762.99 Checkbox: ICD-10: O15 ICD-9: 637.03, 637.04 +SE: 637.10 +DK: 661.3, 762.19, 637.19, 637.99, Checkbox: ICD-10: O11, O14	Adapted ICD-8: ICD-10: O15 Adapted ICD-8: ICD-10: O11, O14	ICD-8: 637.19, 637.99, 762.29, 762.39, 762.99 ICD-9: 642.6 ICD-10: O15 ICD-8: 637.03, 637.04 +SE: 637.10 +DK: 661.3, 762.19, 637.19, 637.99, ICD-9: 642.4, 642.5, 642.7 ICD-10: O11, O14

Abbreviations: DK, Denmark; FI, Finland; GA, gestational age; HELLP, hemolysis, elevated liver enzymes and low platelet count; ICD: International Classification of Diseases LMP, last menstrual period; NO, Norway; SE, Sweden.

TABLE 2 Sex of the first-born and risk of obstetric complications in the second birth

First born	N	Cases	Risk/1000	RD/1000	(95% CI)	RR	(95% CI)
Stillbirth							
Denmark							
Male	321 353	1231	3.83	0.34	(0.04; 0.64)	1.10	(1.01; 1.19)
Female	303 826	1060	3.49	0.00	(reference)	1.00	(reference)
Finland							
Male	194 731	545	2.80	0.24	(−0.09; 0.57)	1.09	(0.97; 1.24)
Female	185 560	475	2.56	0.00	(reference)	1.00	(reference)
Norway							
Male	230 887	918	3.98	0.21	(−0.15; 0.58)	1.06	(0.96; 1.16)
Female	217 647	819	3.76	0.00	(reference)	1.00	(reference)
Sweden							
Male	438 686	1141	2.60	0.27	(0.05; 0.48)	1.11	(1.02; 1.21)
Female	412 768	964	2.34	0.00	(reference)	1.00	(reference)
All							
Male	1 185 657	3835	3.23	0.27	(0.13; 0.41)	1.09	(1.04; 1.14)
Female	1 119 801	3318	2.96	0.00	(reference)	1.00	(reference)
Preterm birth							
Denmark							
Male	321 353	14 787	46.01	3.34	(2.32; 4.36)	1.08	(1.05; 1.10)
Female	303 826	12 967	42.68	0.00	(reference)	1.00	(reference)
Finland							
Male	194 731	7159	36.76	3.11	(1.94; 4.28)	1.09	(1.06; 1.13)
Female	185 560	6245	33.65	0.00	(reference)	1.00	(reference)
Norway							
Male	230 887	10 364	44.89	3.66	(2.47; 4.84)	1.09	(1.06; 1.12)
Female	217 647	8974	41.23	0.00	(reference)	1.00	(reference)
Sweden							
Male	460 668	19 389	42.09	2.91	(2.09; 3.73)	1.07	(1.05; 1.10)
Female	433 372	16 980	39.18	0.00	(reference)	1.00	(reference)
All							
Male	1 207 639	51 699	42.81	3.20	(2.70; 3.71)	1.08	(1.07; 1.09)
Female	1 140 405	45 166	39.61	0.00	(reference)	1.00	(reference)
Preeclampsia/eclampsia							
Denmark							
Male	321 353	5073	15.79	0.79	(0.18; 1.40)	1.05	(1.01; 1.10)
Female	303 826	4555	14.99	0.00	(reference)	1.00	(reference)
Finland							
Male	194 731	3775	19.39	0.86	(0.00; 1.73)	1.05	(1.00; 1.10)
Female	185 560	3437	18.52	0.00	(reference)	1.00	(reference)
Norway							
Male	230 887	5103	22.10	0.46	(−0.40; 1.32)	1.02	(0.98; 1.06)
Female	217 647	4710	21.64	0.00	(reference)	1.00	(reference)
Sweden							
Male	460 668	7177	15.58	0.56	(0.05; 1.07)	1.04	(1.00; 1.07)
Female	433 370	6508	15.02	0.00	(reference)	1.00	(reference)

(Continues)

TABLE 2 (Continued)

First born	N	Cases	Risk/1000	RD/1000	(95% CI)	RR	(95% CI)
All							
Male	1 207 639	21 128	17.50	0.65	(0.32; 0.98)	1.04	(1.02; 1.06)
Female	1 140 405	19 210	16.84	0.00	(reference)	1.00	(reference)
Placental abruption							
Denmark							
Male	321 353	1781	5.54	0.34	(−0.03; 0.70)	1.06	(0.99; 1.14)
Female	303 826	1582	5.21	0.00	(reference)	1.00	(reference)
Finland							
Male	194 731	682	3.50	0.41	(0.05; 0.78)	1.13	(1.02; 1.27)
Female	185 560	573	3.09	0.00	(reference)	1.00	(reference)
Norway							
Male	230 887	1090	4.72	0.25	(−0.15; 0.64)	1.05	(0.97; 1.15)
Female	217 647	974	4.48	0.00	(reference)	1.00	(reference)
Sweden							
Male	460 668	1970	4.28	0.43	(0.17; 0.70)	1.11	(1.04; 1.19)
Female	433 372	1665	3.84	0.00	(reference)	1.00	(reference)
All							
Male	1 207 639	5523	4.57	0.37	(0.20; 0.54)	1.09	(1.05; 1.13)
Female	1 140 405	4794	4.20	0.00	(reference)	1.00	(reference)

Abbreviations: CI, confidence interval; RD, risk difference; RR, relative risk.

Cochran's *Q* and the associated I^2 statistic were used as measures of heterogeneity between the counties.

2.2 | Ethical approval

Data included in the study are summary statistics from each of the participating countries with no linkage to microdata. According to Danish legislation, ethics committee approval is not warranted. The project was conducted under the general approval of the Danish Data Protection Agency to register-based research at Statistics Denmark.

3 | RESULTS

A total of about 2.3 million singleton second births were included in the study. The overall prevalences of the outcomes under study per 1000 second births were 17.2 for preeclampsia/eclampsia, 4.4 for placental abruption, 3.1 for stillbirth, and 41.3 for preterm birth. Compared with having a girl in the first birth, having a boy was associated with the following increases in relative risks in second births: 4% higher (95% CI 2%-6%) for preeclampsia/eclampsia, 9% higher (95% CI 5%-13%) for placental abruption, 9% higher (95% CI 4%-14%) for stillbirth, and 8% higher (95% CI 7%-9%) for preterm birth (Table 2). The analysis of heterogeneity of the risk ratio suggested that the between-country heterogeneity was limited for all outcomes ($P > .05$ for test of Cochrane's *Q*, $I^2 = 0\%$). The population-attributable risks of complications in the second birth, given a first-born boy, were 2.0% (0.97%-2.92%) for preeclampsia/eclampsia, 4.3% (2.38%-6.18%) for placental abruption, 4.5% (2.17%-6.73%) for stillbirth, and 4.0% (3.37%-4.59%) for preterm birth.

4 | DISCUSSION

In pregnancies following a first-born boy, we consistently found slightly increased risks of preeclampsia/eclampsia, placental abruption, stillbirth, and preterm birth. Due to the prevalence of first-born boys, these small increases in risks explain a non-trivial proportion of most of these outcomes in the second pregnancy. The findings also point to biological mechanisms that need to be further explored to increase our understanding of the complications and reveal potential treatment targets.

The Medical Birth Registers in Denmark, Finland, Norway, and Sweden collect data on all births, so there is no selection bias. However, the present study is limited by a lack of knowledge of pregnancies not recorded in the Medical Birth Registers (early pregnancy losses). Due to the definition used in this paper, stillbirths that occur before the 28th completed week of gestation are not included because of differences in national registration

criteria. As early pregnancy losses have been shown to be associated with a first-born boy, we would expect this to bias our findings towards the null.[7] Sex of the first birth is easily measured, but the validity of some of the outcome measurements is not perfect, which will likely also bias the associations towards the null.[8] It has been shown that pregnancies with a male fetus carry an increased risk of preterm birth, stillbirth, preeclampsia, and placental abruption,[9-13] which means that complications in the first pregnancy may act as an intermediary mechanism between sex of the first-born and outcomes in the next pregnancy. Adjusting for intermediary variables will result in biased estimates of the influence of sex of the first-born on obstetric outcome even in the absence of all other biases. The importance of intermediary variables can be estimated, but unfortunately, it is difficult to quantify this because of the added assumptions of mediation analyses.[14]

Our findings could be influenced by confounding from common causes of fetal sex and obstetric complications. As previously argued, this is unlikely. If a confounding factor were to affect sex in the first pregnancy and obstetric complications in the second, such a confounder would likely also by extension affect obstetric complications in the first pregnancy and sex in the second pregnancy. Also, it would likely affect sex in both pregnancies. However, there is no evidence to support that either of these associations exist.[1,15,16] It is still possible to argue for a role for confounding in the absence of such associations, but such arguments remain speculative.[17]

This study confirms and extends previous findings.[1,3] We find it is unlikely that the results are attributable to bias, but the epidemiological data used in this study cannot provide proof of causal pathways. In addition to the role of obstetric complications in the first birth, the effects of sex of the first-born on maternal behavior and/or health are often mentioned, but the evidence in support of such mechanisms is anecdotal and is not supported by findings from observational cohort studies.[1] Any causal explanation would necessitate the existence of some biological memory that can "remember" and so act as the pathway that carries the effect of a first boy on future outcomes. An immunological mechanism could provide such memory. First, the potential of maternal immunity directed at male-specific histocompatibility (H-Y) antigens is well described in the non-physiological situation of stem-cell transplantation. H-Y immunity established in previous pregnancies of female stem-cell transplantation donors is held responsible for the increased risk of graft-vs-host disease in male recipients[18] and H-Y immunity seems to play a causal role in recurrent pregnancy loss.[19] The H-Y killing capacity of H-Y antibodies is well known from research in the milk industry. Culturing of cow embryos in H-Y-high-titer antibodies arrested half of the embryos and subsequent transfer of living embryos resulted in 86% female offspring.[20] Second, the immunological hypothesis is compatible with the lack of tracking of sex across pregnancies. Third, the risk of recurrent obstetric complications is also compatible with the immunological mechanism because all complications included in this study increase transfer of fetal material to the maternal circulation, which again increases the risk of immunization.[21-24]

We suggest that future research should be directed at activities that can explore underlying mechanisms, for example through a reanalysis of some of the major randomized controlled trials on the use of progesterone, immunoglobulin, or other immune-modulating agents during pregnancy. Epidemiological studies that track women over multiple pregnancies may also contribute to the understanding of this association. Since an H-Y-driven mechanism might affect male fetuses more than female fetuses, this should also be explored in further detail under consideration of the risk of collider stratification bias.

5 | CONCLUSION

Based on data from the Nordic Registries including more than 2.3 million second-born children we show a consistent pattern of association across the four countries between sex of the first-born and subsequent risks of obstetric complications. Future research should focus on pathophysiological aspects of this association because it may hold the potential to reduce these poorly understood obstetric complications.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

ORCID

Henriette S. Nielsen https://orcid.org/0000-0003-2106-8103

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