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ORIGINAL RESEARCH

IgA Deficiency, Autoimmunity & Pregnancy: A Population-Based Matched Cohort Study

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Abstract
Background Several autoimmune disorders have been linked to adverse pregnancy outcome. IgA deficiency shares many autoimmune traits, but its association with pregnancy outcome is unknown.
Methods Prospective population-based cohort study in Sweden of 613 mothers with IgA deficiency (IgA levels<.07 g/L) diagnosed in 1980–2010 in six university hospitals. In 1973–2010, these women delivered 1,172 singleton infants registered in the Swedish Medical Birth Register. Each delivery to a woman with IgA deficiency was matched on maternal age, parity, early pregnancy smoking status, education level, and delivery year with up to 5 control births (n=5,758).
Results Offspring to women with IgA deficiency had 79 g lower birth weight than controls (mean±SD: 3,457±559 vs 3,537±553 g, P<0.001), and 1.4 days shorter gestational age (mean±SD: 278±13 vs 280±14 days, P=0.001). No difference in preterm birth (<37 weeks) could be detected in deliveries to women with IgA deficiency vs control deliveries (5.8 % vs 5.2 %; odds ratio (OR)=1.13, 95%CI=0.85–1.49), but small for gestational age birth was more common (4.3 % vs 2.8 %; OR=1.48, 95%CI=1.04–2.10). Women with IgA deficiency also delivered more often by caesarean section (16.9 % vs 11.9 %; OR=1.51, 95%CI=1.26–1.82), while no difference was observed regarding low Apgar score (<7 at 5 min; 1.1 % vs 1.0 %; OR=1.18; 95%CI=0.62–2.27). When excluding women with autoimmune diseases, the excess risks of adverse pregnancy outcome diminished.
Conclusion There is a small excess risk of certain adverse delivery and perinatal outcomes among offspring to women with IgA deficiency. These excess risks are attenuated when considering the presence of autoimmune diseases.

Keywords Autoimmune · childbirth · IgA deficiency · immunoglobulin · pregnancy · perinatal outcomes

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Introduction

Selective IgA deficiency is an immunodeficiency that is characterized by total IgA levels <0.07 g/L,[1] which occurs in about 1:200–600 Caucasians. IgA is instrumental for the mucosal immune defense, and has been linked to recurrent respiratory and gastrointestinal infections [2–4]. In addition to an excess risk of infections, individuals with IgA deficiency seem to be at increased risk of death [5] and autoimmunity [6].

According to WHO estimates, one in ten newborns is born preterm (<37 completed gestational weeks) [7], and more than 1 million children die from preterm birth complications each year. Besides an increased neonatal mortality [8], preterm birth and especially very preterm birth (<33 completed gestational weeks) has been linked

to cognitive dysfunction (e.g. poor attention, and executive functions) [9, 8]. Other adverse pregnancy outcomes include low birth weight and intrauterine growth retardation. Both preterm birth and poor intrauterine growth are inversely related to full-scale IQ, and skills in reading, spelling, and math [10]. Also the risk of bronchopulmonary dysplasia, intraventricular haemorrhage, retinopathy of prematurity, and poor growth later in childhood are influenced [11, 12, 8] by preterm birth and birth weight. Finally, preterm birth and low birth weight are a trauma for the whole family and can have negative psychosocial effects [13].

Several autoimmune disorders have been linked to an increased risk of adverse pregnancy outcome [14–18]. These include celiac disease [19], which often constitutes the reason for measuring total IgA subsequently leading up to an IgA deficiency diagnosis. Furthermore, because of the susceptibility for infectious disease among women with IgA-deficiency, this immunodeficiency may be linked to an increased risk of premature contractions and premature rupture of the membranes (PROM) leading to preterm birth. However, we are not aware of any study examining IgA deficiency in the pregnant mother and pregnancy outcome.

This study aimed to quantify the risk of adverse pregnancy outcome in a population-based cohort of mothers with confirmed IgA deficiency.

Methods

Setting

In Sweden, antenatal and delivery care is provided for free, with a participation rate in the antenatal care program close to 100 %. The first visit commonly takes place at the end of the first trimester [20].

Register Linkage

The Swedish Medical Birth Register includes information on >98 % of all births in Sweden since 1973. Starting at the first antenatal visit, information is prospectively collected, using standardized pregnancy, delivery and infancy records.[21]

Data from the Medical Birth Register were linked to a clinical database of patients with diagnosed IgA deficiency. Thereafter the analyses were performed on the delivery level, as the same woman could contribute more than one delivery during the study period. We excluded multiple births since they differ in duration of gestation and fetal growth, as well as having a higher occurrence of pregnancy and perinatal complications [22].

Covariates

We retrieved data on maternal age, parity, maternal country of birth, early pregnancy smoking status (data available from 1982), body mass index (BMI; data available from 1992), and delivery year from the Medical Birth Register. At the first antenatal visit, smoking habits were registered, based on self-reported cigarette consumption (non-smoker, 1–10, >11 cigarettes per day). Maternal education level was retrieved from the Education Register at Statistics Sweden and classified as ≤9, 10–12, and >13 years. Country of birth of the mother was categorized into Nordic and non-Nordic, with Sweden, Denmark, Norway, Finland, and Iceland being the Nordic countries.

IgA Deficiency Cohort

Women with IgA deficiency were identified from laboratory data from 1980 through 2010 at six university hospitals in Sweden (Karolinska Hospital in Stockholm, Sahlgrenska hospital in Gothenburg, the University hospital in Lund, the University hospital in Linköping, the University hospital in Umeå and the Academic hospital in Uppsala). These university hospitals cater for both urban and rural areas.

We defined IgA deficiency as having an IgA value <0.07 g/L, with normal IgM and IgG levels, in individuals ≥4 years of age in accordance with the recommendations of the International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies.[23] In the current study we required that all study participants had a low IgA value (below or equal to 0.07 g/L) recorded after the age of 10 years. Only if levels are persistently low after the age of 10 years can IgA deficiency be diagnosed accurately since younger children may still have transiently low IgA values between 4 and 10 years of age.[24] In Sweden, most laboratories use nephelometry to measure total IgA levels. In this study we regarded pregnancies to women who at some stage after 10 years of age had IgA deficiency as exposed (both those with diagnosed IgA deficiency before pregnancy and those diagnosed after pregnancy, since almost all IgA deficiency is prevalent since childhood even if diagnosed later).

Women with IgA deficiency were then linked to the Swedish Medical Birth Register to identify those who had delivered singleton infants between 1973 and 2010.

Control Births

Five control births per delivering woman with IgA deficiency were sampled from the Swedish Medical Birth Register matched on maternal age (±1 year), early pregnancy smoking

status (non-smoker/1–10/≥11 cigarettes per day/missing), education level (≤9/10–12/≥13 years/missing), parity (nulliparous/parous), country of birth (Nordic/non-Nordic), and delivery year (±1 year). If a full five matched control births could not be found, the IgA patients and their controls were still included. If no matched control births could be identified, the IgA patients were excluded (n=8).

Presence of autoimmune diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, celiac disease, systemic lupus erythematosus, myasthenia gravis, hypothyroidism, hyperthyroidism, and type 1 diabetes, was determined via visits in inpatient (1968–2010) and nonprimary outpatient care (2001–2010) based on the first main diagnosis listing for any of the diseases.

A secondary control cohort was also matched using the same matching factors, but requiring both patients with IgA deficiency and controls to be free of autoimmune diseases during follow-up.

Outcome

The primary outcome measures were preterm birth and birth weight for gestational age.

Preterm birth was defined as <37 completed weeks of gestation [25]. Gestational age was determined by ultrasound, or, if unavailable, the recorded date of the first day of the last menstrual period. Since 1990, Swedish women are routinely offered early second trimester ultrasonography to estimate gestational age, and approximately 95 % accept this offer [26].

Ultrasound-based Swedish reference curves for fetal growth were used [27]. Large- and small-for-gestational-age were defined as a birth weight of >2 standard deviations above or below the mean for gestational age and sex.

Secondary outcomes were pregnancy duration, birth weight (mean; low/very low corresponding to <2,500 g/<1,500 g), Apgar score <7 at 5 min, caesarean section, and stillbirth.

Statistics

Singleton births to women with IgA deficiency were compared to matched control births without known IgA deficiency.

We estimated risks and risk differences for the selected outcomes. Also, using logistic regression, adjusting for the matching factors, we estimated odds ratios for the outcomes. Potential interactions between the matching factors were handled by conditioning the analyses on these factors.

In our main analyses we examined births to women with IgA deficiency, irrespective of the date of diagnosis for IgA deficiency. In sub-analyses, we looked at pregnancy outcome in women with IgA deficiency diagnosis recorded before delivery, in women with BMI recorded (adjusting for BMI in the logistic regressions), and in women without an autoimmune disease diagnosis prior to delivery (using the secondary matched control group). For relevant diagnostic codes see Table VII.

Data were analyzed using SAS (version 9.4). Reported P-values are two-sided and P-values <0.05 were considered statistically significant.

Results

We identified 1,404 women who had been diagnosed with IgA deficiency at any of the participating university hospitals between 1980 and 2012. Of these individuals, 622 women had 1,226 registered births in the Medical Birth Register between 1973 and 2010. Multiple births were excluded resulting in 1,180 singleton births to 613 unique mothers. For these 1,180 singleton births, matched control births were found for 1,172, making up the analysis dataset.

Maternal Characteristics

The mean maternal age at delivery was 29 years (range: 16–44 years), while the mean age at IgA deficiency diagnosis was 38 years (range: 2–76 years). 26 % of the deliveries occurred after the IgA deficiency diagnosis, 45 % of the deliveries were to nulliparous women, and 95 % in women born in the Nordic countries (Table I). Among women with data on smoking, 19 % were smokers. No difference in BMI was detected between patients with IgA deficiency and matched controls (P=0.35).

Pregnancy Duration and Preterm Birth

The pregnancy duration in women with IgA deficiency was on average 1.4 days shorter than in matched control births (95 % CI: 0.6–2.3; P=0.001; Fig. 1), but no significant difference in the risk of preterm birth was detected between IgA deficiency cases and matched controls (5.8 % vs 5.2 %; risk difference 0.6 %, 95 % CI: −0.8 to 2.1; Table II).

Fetal Growth and Birth Weight

Mean birth weight was 79 g lower in women with IgA deficiency than in matched control births (95 % CI: 44–114; P<0.001; Fig. 2). Also, the risk of small for gestational age birth was higher in IgA deficiency cases than matched controls (4.3 % vs 2.8 %; risk difference 1.5 %, 95 % CI: 0.3–2.8; OR=1.48, 95 % CI: 1.04–2.10), and the risk of low birth

Table I Singleton birth and maternal characteristics

	Births to women with IgA deficiency n=1,172	Matched control births n=5,758
Maternal age at delivery, mean (SD) (years)	29 (5)	29 (5)
Age at IgA deficiency diagnosis, mean (SD)	38 (12)	–
Body mass index, mean (SD) [1992–2010]	23.8 (4.3)	24.0 (4.2)
Missing [1992–2010], *n* (%)	101 (17 %)	437 (15 %)
Smoking status, *n* (%) [1982–2010]		
Non-smoker	662 (81 %)	3,292 (81 %)
1–10 cigarettes per day	97 (12 %)	461 (11 %)
>10 cigarettes per day	61 (7 %)	292 (7 %)
Missing	85	382
Nulliparous, *n* (%)	528 (45 %)	2,585 (45 %)
Education level[a] (years), *n* (%)		
≤9	143 (12 %)	695 (12 %)
10–12	593 (51 %)	2,953 (51 %)
>12	433 (37 %)	2,104 (37 %)
Missing	3 (0 %)	6 (0 %)
Non-Nordic country of birth,[b] *n* (%)	61 (5 %)	277 (5 %)
Delivery year, *n* (%)		
1973–1979	206 (18 %)	1,013 (18 %)
1980–1989	264 (23 %)	1,330 (23 %)
1990–1999	371 (32 %)	1,791 (32 %)
2000–2010	331 (28 %)	1,624 (28 %)
Autoimmune disease,[c] *n* (%)	302 (26 %)	332 (5.8 %)

a Highest reported level based on data from 1990, 1995, 2000, 2005, and 2009

b Mother born outside Sweden, Denmark, Norway, Finland, and Iceland

c Inpatients (1968–2010) or nonprimary outpatient (2001–2010) care visits listing an autoimmune disease

weight was 4.5 % vs 3.3 % (risk difference 1.1 %, 95 % CI: −0.1 to 2.4; Table II). No difference was observed for large for gestational age birth (Table II).

Delivery Outcomes

Caesarean section was more common in births to women with IgA deficiency than in matched control births (16.9 % vs 11.9 %; risk difference 5.0 %, 95 % CI: 2.6–7.3; Table II). The corresponding odds ratio was 1.51 (95 % CI: 1.26–1.82). No difference was detected in Apgar score at 5 min or stillbirth (Table II).

Subgroup Analyses

IgA Deficiency Diagnosis Before Delivery When analyzing the subgroup of women with an IgA deficiency diagnosis before delivery (n=299; 26 %), the point estimate for the risk difference for small for gestational age was 2.2 %, but did not reach statistical significance (95 % CI: −0.4 to 4.7; Table III). The risk of delivering by caesarean section also remained elevated and the risk difference was of similar magnitude as in the main analysis, but did not reach statistical significance (4.7 %, 95 % CI: −0.3 to 9.7; Table III).

BMI In the subgroup of births to women with BMI information (n=634; 54 %), the risk of caesarean section remained elevated compared to matched controls (risk difference 5.4 %, 95 % CI: 2.1–8.7), but small for gestational age did not (Table IV).

Autoimmunity Women with IgA deficiency and autoimmune diagnosis listed during the study period had a higher risk of caesarean section compared to women with IgA deficiency without autoimmune disease listed (Fig. 3).

In the subgroup of women with IgA deficiency but without autoimmune disease listed (n=870; 74 %), birth weight remained lower than in matched controls (Table V) but none of the adverse pregnancy outcomes reached statistical significance (odds ratio for small for gestational age: 1.35, 95 % CI: 0.90–2.02; and caesarean section: 1.23, 95 % CI: 0.98–1.54) (Table VI).

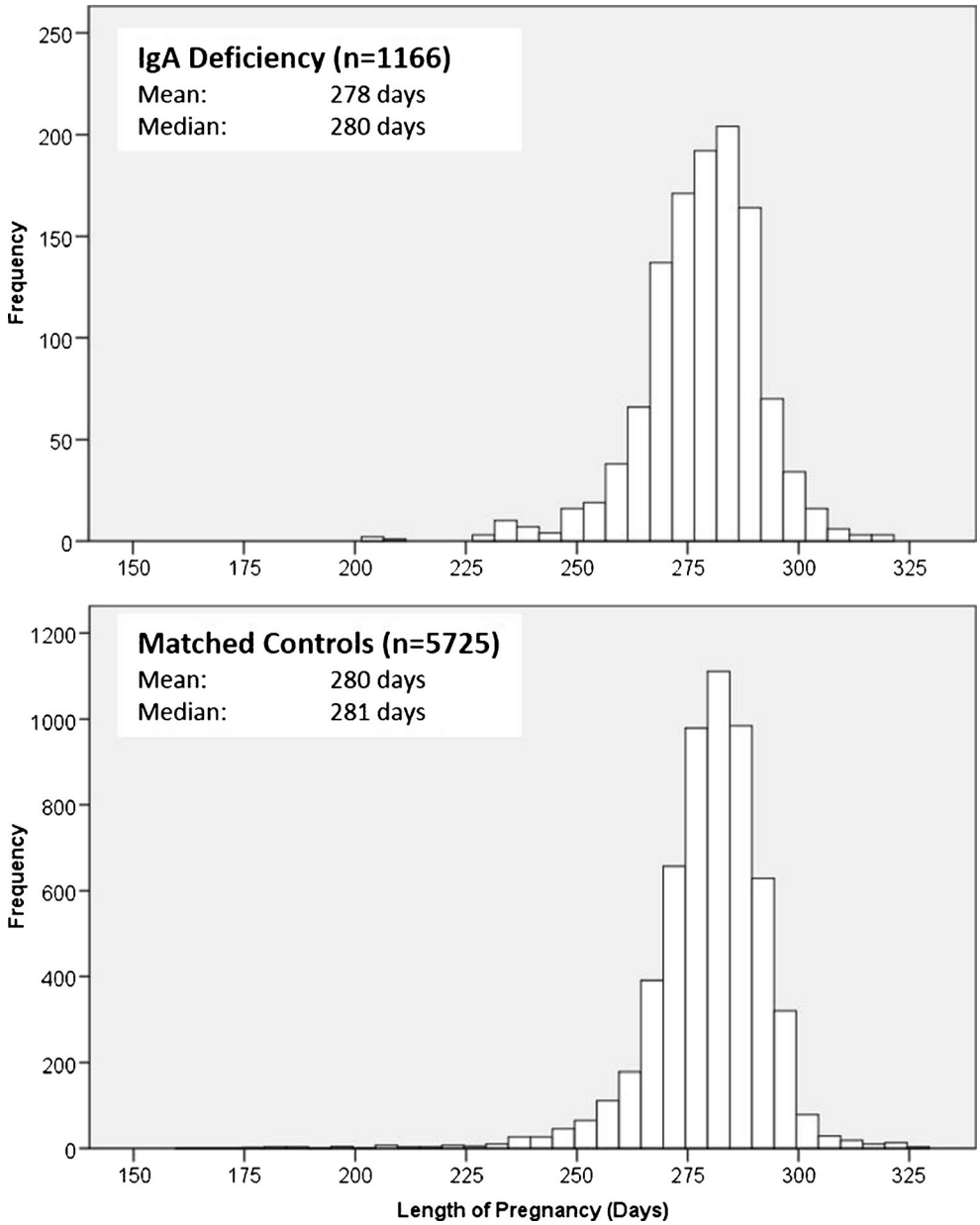

Fig. 1 Distribution of length of pregnancy in live births to women with IgA deficiency and matched controls

Discussion

This population-based cohort study of more than 1,000 births to women with IgA deficiency detected an increased risk for small for gestational age birth, but not for preterm birth. Among our secondary outcomes, IgA deficiency in the mother was linked to an increased risk of cesarean section, but no differences in low Apgar score at 5 min or stillbirth were detected.

We found broadly similar risk estimates in women diagnosed with IgA deficiency before delivery and in those diagnosed after delivery, although the precision was lower for the smaller group of women diagnosed with IgA deficiency before delivery. Limited statistical power may also explain why diagnosed IgA deficiency was not statistically significantly associated with small for gestational age despite the fact that the relative risk was 1.79 in this group compared to an overall relative risk of 1.48. Of note, the moderately increased risks for small for gestational age and cesarean section, both diminished when we considered the presence of autoimmune disease.

Previous Research and Potential Mechanisms of Action

We performed a PubMed English language literature search for ["IgA deficiency" AND (pregnancy or childbirth)] (n=34 hits). With the exception of case reports of pregnant women with both IgA deficiency and thromobocytopenia [28], or

Table II Perinatal and delivery outcomes in births[d] to women with diagnosed IgA deficiency and matched control pregnancies

Outcome	Individuals analysed (*n*)		Cases, *n* (%)		IgA deficiency versus matched controls	
	IgA deficiency	Matched controls	IgA deficiency	Matched controls	Risk difference (95 % CI)	Odds ratio[e] (95 % CI)
Preterm birth (<37 weeks of gestation)	1,166	5,725	68 (5.8 %)	298 (5.2 %)	0.6 % (−0.8 to 2.1)	1.13 (0.85–1.49)
Small-for-gestational-age <2 SD for sex and gestational age	1,161	5,714	50 (4.3 %)	160 (2.8 %)	1.5 % (0.3 to 2.8)	1.48 (1.04–2.10)
Large-for-gestational-age >2 SD for sex and gestational age	1,161	5,714	37 (3.2 %)	189 (3.3 %)	−0.1 % (−1.2 to 1.0)	1.02 (0.71–1.48)
Low birth weight (<2,500 g)	1,162	5,722	52 (4.5 %)	191 (3.3 %)	1.1 % (−0.1 to 2.4)	1.40 (1.01–1.96)
Very low birth weight (<1,500 g)	1,162	5,722	4 (0.3 %)	24 (0.4 %)	−0.1 % (−0.5 to 0.3)	1.03 (0.34–3.08)
Caesarean section	1,167	5,733	197 (16.9 %)	684 (11.9 %)	5.0 % (2.6–7.3)	1.51 (1.26–1.82)
Apgar <7 at 5 min	1,106	5,404	12 (1.1 %)	56 (1.0 %)	0.1 % (−0.6 to 0.7)	1.18 (0.62–2.27)
Stillbirth	1,172	5,758	5 (0.4 %)	25 (0.4 %)	0.0 % (−0.4 to 0.4)	1.12 (0.42–2.98)

All outcomes analysed in live births, except for stillbirth

Conditioned on the matching factors and adjusted for maternal age

angiooedema [29] we could not identify any literature on IgA deficiency and pregnancy outcome. When Petty et al. screened 28,000 pregnant women for IgA deficiency they detected 61 IgA deficient mothers (1:459), but their paper contained no information on the outcome of pregnancy or the offspring [30].

IgA deficiency is strongly linked to autoimmune diseases [6, 31] and women with rheumatoid arthritis [15, 32], systemic lupus erythematosus [14, 32], type 1 diabetes [18], and celiac disease [19, 33, 34] are all at increased risk of adverse pregnancy outcome. Although disease-specific causes for adverse pregnancy outcome (for example I. neonatal macrosomia caused by hyperglycemia in Type 1 diabetes, II. neonatal lupus caused by lupus antibodies, and III. various consequences of steroid use in pregnant women with rheumatoid arthritis) may not be relevant to IgA deficient pregnant mothers, earlier research in autoimmune disease may still have implications for pregnancy in women with IgA deficiency.

Women with rheumatoid arthritis are at increased risk of both preterm birth and intrauterine growth retardation [15]. While the current study found no statistically significant risk of preterm birth (OR=1.13), it found a 48 % increased risk of small for gestational age birth. Some 4.3 % of women with IgA deficiency (vs. 2.8 % of reference women) had offspring small for gestational age birth. This is important as small for gestational age birth has been linked to an increased risk of both neonatal and post-neonatal mortality [35]. In addition, small for gestational age birth children have a poorer neuropsychological development and lower IQ [36].

Consistent with the increased risk of small for gestational age birth, women with IgA deficiency were also at increased risk of giving birth to low birth weight infants (OR=1.40), although it should be underlined that the mean birth weight difference was only 79 g.

Finally, IgA deficiency in the pregnant mother was associated with a 1.51-fold increased risk of cesarean section. Some 16.9 % of IgA deficient mother had a cesarean section. From an international perspective this is a low figure, but still higher than the 11.9 % of matched reference women. The long study period (stretching from 1973 and onwards, when caesarean section was less common than today) as well as the traditionally low caesarean section rates in Sweden may explain the low caesarean section rate in this study.

Strengths and Limitations

Among the main strength of this paper are the definition of IgA deficiency (all individuals had undergone measurement of total IgA <0.07 g/L), and the large number of patients allowing for sub-analyses and the examination of outcomes that occur in less than 10 % of pregnancies. For instance, this study included 72 preterm offspring to women with IgA deficiency, and 56 offspring with low birth weight. The great statistical power allowed us to detect even minor risk increases such as the 79 g lower mean birth weight in offspring to women with IgA deficiency. At the same time, we had the power to *rule out* a major risk increase for preterm birth as the 95 % CI upper OR interval was only 1.49. Of little clinical importance, is the fact that we were able to show that IgA deficiency pregnancy had a statistically significantly shorter duration (minus 1 day) than reference pregnancies also demonstrate the statistical power of our study.

Another strength is our use of the nationwide Swedish Medical Birth Register. This register contains antenatal and perinatal data on >98 % of all births in Sweden since 1973 [21]. A recent validation of the Medical Birth Register found that the majority of the variables in the register are of high quality [37]. Data are collected prospectively on standardized

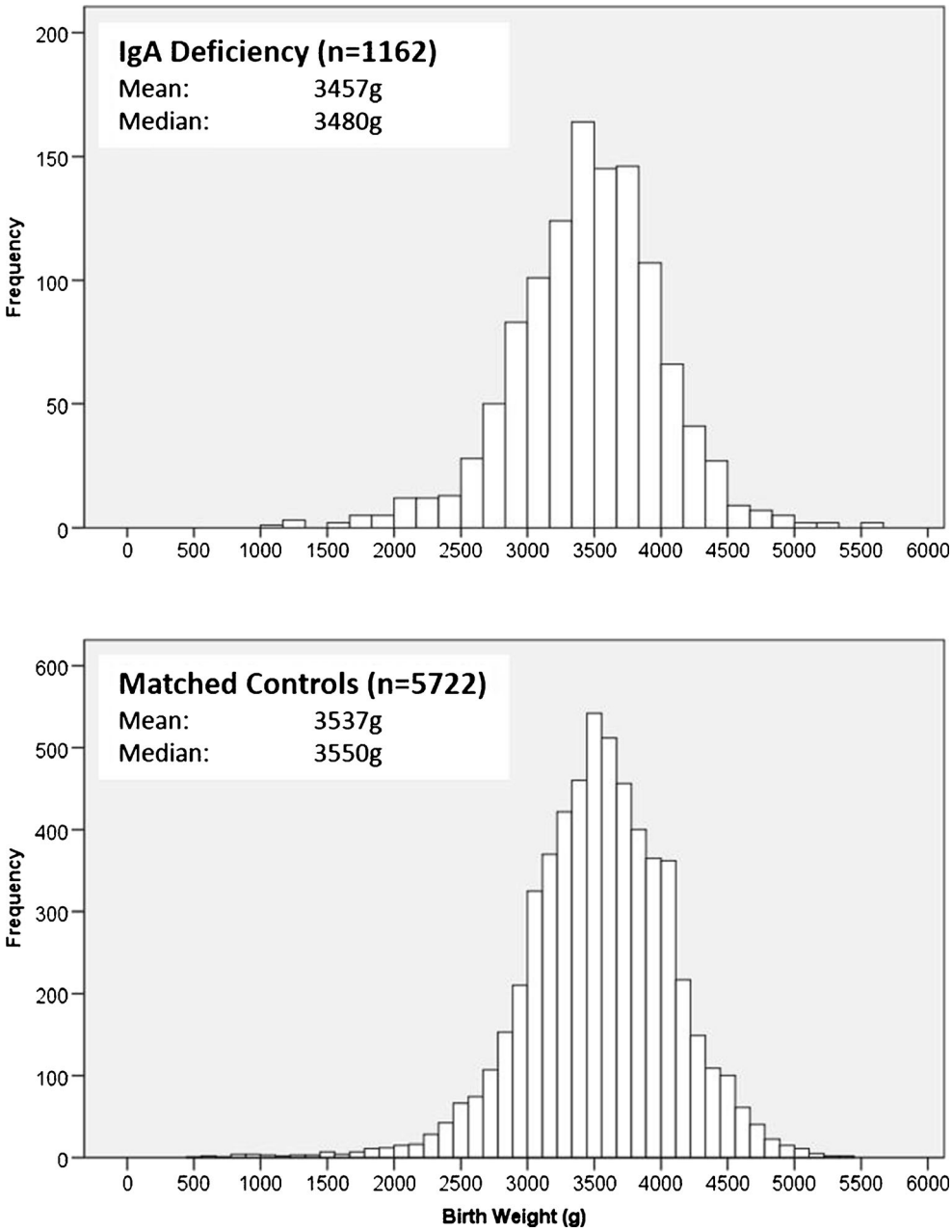

Fig. 2 Distribution of birth weight in live births to women with IgA deficiency and matched controls

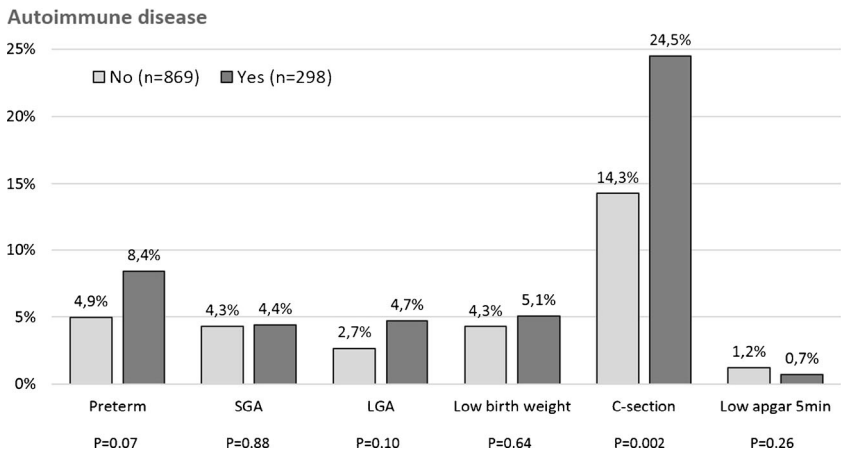

Fig. 3 Perinatal and pregnancy outcomes in live births to women with IgA deficiency with vs without autoimmune diagnoses SGA, small for gestational age. LGA, Large for gestational age. C-section, cesarean section. *P*-values: From conditional logistic regression models adjusted for maternal age, and conditioned on smoking, parity, country of birth, education level, and delivery year

forms starting at the first antenatal health visit, and variables include smoking and BMI. Matching for smoking is important since smoking influences preterm birth rates [38, 39] but may be inversely associated with IgA deficiency. Through the Swedish National Patient Register [40] we were able to identify mothers with comorbidity. Of special interest is celiac disease since many patients with IgA deficiency are identified as part of the work-up for celiac disease [41]. This study shows that autoimmune comorbidity is likely to have contributed to the excess risk of certain pregnancy complications seen in women with IgA deficiency. In a subgroup analysis of women without register-detected autoimmune diseases risk estimates did not attain statistical significance. However, it should be noted that the risk estimates were generally similar in this sub-analysis to the findings in the overall analysis, but the statistical power was lower (with widening 95 % confidence intervals as a consequence). Still, caesarean section was more common in patients with than without autoimmune disease.

Because Sweden does not routinely screen all residents for IgA deficiency we cannot rule out that a number of controls have false-negative IgA deficiency. This is however unlikely to have more than a minor effect on risk estimates since the prevalence of IgA deficiency is <0.2 % in the general population.[24]

Conclusion

In conclusion, this study found a small excess risk of certain adverse delivery and perinatal outcomes among offspring to women with IgA deficiency. These excess risks were attenuated when considering the presence of autoimmune diseases.

Acknowledgments

Competing interest statement The authors (JFL, MN, OS, LH) declare that they have no conflicts of interest relevant to the contents of this manuscript.

Details of contributors Dr Ludvigsson and Dr Neovius had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ludvigsson, Neovius, Hammarström, Stephansson

Acquisition of data: Ludvigsson, Hammarström

Drafting of the manuscript: Ludvigsson, Neovius

Critical revision of the manuscript for important intellectual content: Hammarström, Ludvigsson, Neovius, Stephansson

Statistical analysis: Ludvigsson, Neovius

Obtained funding: Hammarström

Ethical approval This project (2011/69–31/3) was approved by the Regional Ethical Review Board in Stockholm on Feb 23, 2011. This was a register-based study and therefore all data were anonymized prior to analysis, and we were not allowed to contact the patients.

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Statement of independence of researchers from funders No person representing the funding sources read or commented on any version of the manuscript.

Appendix

Table III Perinatal and delivery outcomes in births to women with diagnosed IgA deficiency before delivery and matched control pregnancies

Outcome	Individuals analysed (*n*)		Cases, *n* (%)		IgA deficiency versus matched controls	
	IgA deficiency	Matched controls	IgA deficiency	Matched controls	Risk difference (95 % CI)	Odds ratio[a] (95 % CI)
Preterm birth (<37 weeks of gestation)	298	1,494	17 (5.7 %)	91 (6.1 %)	−0.4 % (−3.3 to 2.5)	0.95 (0.55–1.67)
Small-for-gestational-age <2 SD for sex and gestational age	296	1,490	14 (4.7 %)	38 (2.6 %)	2.2 % (−0.4 to 4.7)	1.79 (0.88–3.63)
Large-for-gestational-age >2 SD for sex and gestational age	296	1,490	14 (4.7 %)	53 (3.6 %)	1.2 % (−1.4 to 3.8)	1.53 (0.79–2.96)
Low birth weight (<2,500 g)	296	1,491	12 (4.1 %)	58 (3.9 %)	0.2 % (−2.3 to 2.6)	1.16 (0.59–2.28)
Caesarean section (live births)	298	1,494	63 (21.1 %)	246 (16.5 %)	4.7 % (−0.3 to 9.7)	1.40 (1.01–1.95)
Apgar <7 at 5 min	297	1,478	4 (1.4 %)	14 (1.0 %)	0.4 % (−1.0 to 1.8)	1.89 (0.56–6.34)
Stillbirth	299	1,502	1 (0.3 %)	8 (0.5 %)	−0.2 % (−1.0 to 0.6)	0.75 (0.08–6.61)

Table IV Perinatal and delivery outcomes in births to women with diagnosed IgA deficiency and matched control pregnancies in women with available data on body mass index (BMI). Analyses are adjusted for BMI

Outcome	Individuals analysed (*n*)		Cases, *n* (%)		IgA deficiency versus matched controls	
	IgA deficiency	Matched controls	IgA deficiency	Matched controls	Risk difference (95 % CI)	Odds ratio[a] (95 % CI)
Preterm birth (<37 weeks of gestation)	633	3,261	41 (6.5 %)	169 (5.3 %)	1.2 % (−0.8 to 3.3)	1.28 (0.88–1.86)
Small-for-gestational-age <2 SD for sex and gestational age	631	3,259	22 (3.5 %)	86 (2.7 %)	0.8 % (−0.7 to 2.3)	1.14 (0.66–1.97)
Large-for-gestational-age >2 SD for sex and gestational age	631	3,259	22 (3.5 %)	100 (3.1 %)	0.4 % (−1.2 to 1.9)	1.24 (0.75–2.05)
Low birth weight (<2,500 g)	631	3,260	28 (4.4 %)	101 (3.2 %)	1.3 % (−0.4 to 3.0)	1.50 (0.94–2.41)
Caesarean section (live births)	633	3,215	118 (18.6 %)	426 (13.3 %)	5.4 % (2.1–8.7)	1.42 (1.11–1.81)
Apgar <7 at 5 min	631	3,182	5 (0.8 %)	31 (1.0 %)	−0.1 % (−0.4 to 0.3)	0.73 (0.09–6.19)
Stillbirth	634	3,224	1 (0.2 %)	8 (0.3 %)	−0.1 % (−0.4 to 0.3)	0.73 (0.09–6.19

Table V Pregnancy duration and birth weight in live births

	Live births to women with IgA deficiency	Matched control births	Mean difference (95%CI)
Pregnancy duration (days), n	1,166	5,725	
Mean (SD)	278 (13)	280 n	1.4 (0.6–2.3), *P*=0.001
Median	280	281	–
Minimum-maximum	204–321	162–328	–
Birth weight (g), n	1,162	5,722	
Mean (SD)	3,457 (559)	3,537 (553)	79 (44–114), *P*<0.001
Median	3,480	3,550	–
Minimum-maximum	1,011–5,600	525–5,370	–
Women without autoimmune diagnosis			
Pregnancy duration (days), n	868	4,237	
Mean (SD)	278.8 (13.0)	279.3 (13.5)	0.5 (−0.5 to 1.5), *P*=0.29
Median	280	281	
Minimum-maximum	204–321	162–328	
Birth weight (g), n	866	4,242	
Mean (SD)	3,470 (550)	3,521 (559)	51 (10–91), *P*=0.02
Median	3,500	3,540	
Minimum-maximum	1,265–5,600	525–5,710	

Table VI Perinatal and delivery outcomes in births to women with diagnosed IgA deficiency and matched control pregnancies in women without any autoimmune diagnosis (ever during follow-up)

Outcome	Individuals analysed (*n*)		Cases, *n* (%)		IgA deficiency versus matched controls	
	IgA deficiency	Matched controls	IgA deficiency	Matched controls	Risk difference (95 % CI)	Odds ratio[a] (95 % CI)
Preterm birth (<37 weeks of gestation)	868	4,237	43 (5.0 %)	203 (4.8 %)	0.2 % (−1.4 to 1.8)	1.03 (0.72–1.48)
Small-for-gestational-age						
<2 SD for sex and gestational age	865	4,229	37 (4.3 %)	132 (3.1 %)	1.2 % (−0.3 to 2.6)	1.35 (0.90–2.02)
Large-for-gestational-age >2 SD for sex and gestational age	865	4,229	23 (2.7 %)	136 (3.2 %)	−0.6 % (−1.8 to 0.6)	0.85 (0.54–1.35)
Low birth weight (<2,500 g)	866	4,242	37 (4.3 %)	138 (3.3 %)	1.0 % (−0.4 to 2.5)	1.33 (0.89–1.99)
Caesarean section (live births)	869	4,250	124 (14.3 %)	515 (12.1 %)	2.2 % (−0.4 to 4.7 %)	1.23 (0.98–1.54)
Apgar <7 at 5 min	820	4,019	10 (1.2 %)	44 (1.1 %)	0.1 % (−0.7 to 0.9)	1.35 (0.66–2.78)
Stillbirth	870	4,267	1 (0.1 %)	17 (0.4 %)	−0.3 % (−0.6 to 0.0)	0.33 (0.04–2.60)

Table VII International classification of disease codes

Diagnosis	ICD-10 (1997/1998-)	ICD-9 1987–1997/1998	ICD-8 <1987
Rheumatoid arthritis	M05, M06, M08, M12.3	714	712.3 and 714.93
Crohn's disease	K50	555	563.00
Ulcerative colitis	K51	556	563.10
SLE	M32	710A	734.1
Myasthenia gravis	G70	358A	733
Hypothyreosis	E03	244X, 244 W	244.09
Hyperthyreosis	E05	242	242
Celiac disease	K90	579	269.0
Type 1 diabetes mellitus	E10	250	250

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