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Summary

We assessed maternal serum levels of total immunoglobulin E (IgE) in the first, second and third trimester and changes in total IgE levels from first to third trimester in relation to offspring sex. Within a cohort of 29,948 pregnant women, 392 women without a history preeclampsia and with a live born child were randomly selected. Information on offspring sex was obtained through linkage to the Medical Birth Registry of Norway. Blood samples from each trimester were analysed for total IgE concentration. Differences in mean levels according to offspring sex were estimated. Also changes in total IgE levels from first to third trimester were assessed. In all three trimesters there was a tendency of women carrying a male fetus to have higher mean total IgE level, but significant statistical differences were not reached. The total IgE concentration decreased during pregnancy, but the decrement was lesser in women carrying a male fetus compared to those who carried a female fetus.

Introduction

Previous studies have suggested that asthmatic women carrying a female fetus experience a worsening of their asthma symptoms during pregnancy compared to those carrying a male fetus, (1,2). However, the course of asthma during pregnancy shows variation and the women may experience that their asthma improves, worsens or remains unchanged (3). There is also a variation in the asthma course in successive pregnancies, with nearly half the women experiencing changes in the asthma course between pregnancies (3), suggesting that there might be some factor unique to each pregnancy influencing the asthma outcome.

Immunoglobulin E (IgE) has been closely linked to atopic asthma, and may also play a role in non-atopic asthma in many studies (4-6). It has been demonstrated that increased levels of total serum IgE (7) or cockroach-specific IgE (8) are associated with worsening of asthma symptoms during pregnancy. In addition, asthma exacerbations were associated with increasing or unchanged maternal IgE level, while the IgE level in women without asthma tended to decrease during pregnancy (7).

Knowledge on possible differences in IgE levels in pregnancy according to offspring sex may shed light on the biological mechanisms causing worsening of asthma in women carrying a female fetus. Our aim was to compare maternal levels of total IgE in first, second and third trimester according to the sex of the fetus.

Material and Methods

Between June 1992 and May 1994, 35,940 women in Norway participated in a prospective study of *Toxoplasma gondii* infection in pregnancy (9). The study population included nearly all pregnant women from eleven out of nineteen

counties in Norway. Subsequent to the original study, we attempted to contact all women by mail to obtain their consent to use the collected data for additional scientific purposes and 29,948 women consented. In this population, mean age at childbearing was 29 years (standard deviation [SD] 5.3 years). Forty-one percent of the women were nulliparous, 36 percent were primiparous, and 23 percent of the women had two or more previous deliveries. The women were included at their first antenatal visit to the primary health care, around the 10th week of gestation (mean 10.2 weeks) and additional blood samples were requested at week 22 and 38 in pregnancy. Information on preeclampsia, offspring vital status and sex was obtained through linkage by a unique personal identification number to the Medical Birth Registry of Norway (www.uib.no/mfr). This nation-wide registry has recorded information on all births in Norway since 1967, and information on each pregnancy is obtained by compulsory notification on standardized forms completed by midwives at the delivery ward within one week after delivery.

After linkage to the Medical Birth Registry a random sample of 400 women without preeclampsia with a live born child were drawn and after excluding 8 women with twin pregnancies, 392 women were included in our study (10). These women were also used as controls in a study of the association of maternal total IgE with preeclampsia risk and they did not differ from the original cohort in age, parity or in the distribution of offspring sex.

Among the 392 women, 364 had a blood sample available from first trimester (mean 10.1 weeks, SD 2.9 weeks), 330 from second trimester (mean 23.4 weeks, SD 2.7 weeks) and 266 women had a sample from the third trimester (mean 37.9 weeks, SD 1.2 weeks).

Total IgE levels (in kilounits per liter [kU/L]) were measured on a ImmunoCAP 1000 analyzer using UniCAP[®] kits (Phadia, Uppsala, Sweden). The detection limit is 2 kU/L. Normal values have been determined by the producer on the basis of 63 non-atopic blood donors and the geometric mean was 17.4 kU/L (+2SD =113 kU/L). Mean concentrations of maternal serum total IgE were assessed for all three trimesters for women with male and female offsprings respectively and differences were tested with Student's T-test. We also calculated the mean change in maternal total IgE concentration from first trimester to third trimester according to offspring sex. In addition, proportions of subjects with total IgE levels above 150 kU/L, which is considered an elevated level according to normal reference values, were compared. The statistical analyses were performed using the Statistical Package for the Social Sciences, version 14.0 (SPSS Inc, Chicago, Ill).

The study was approved by the Norwegian National Board of Health, the Norwegian Data Inspectorate, and the Regional Committee for Ethics in Medical Research.

Results

In all three trimesters mean serum levels of total IgE were higher in women with a male offspring than in women with a female offspring (table 1), but the differences were not statistically significant. First trimester: male 101.2 kU/L versus female 92.5 kU/L, $p=0.73$, second trimester: male 73.2 kU/L versus female 67.5 kU/L, $p=0.72$, and third trimester: male 89.2 kU/L versus female 68.5 kU/L, $p=0.40$. Also the proportion of subjects with total IgE level above 150 kU/L was non-significantly higher in women carrying a male fetus.

We studied serial changes in total IgE in subjects on whom we had data on serum total IgE in both first and third trimester. The mean total IgE levels decreased during pregnancy.

Additionally the decrease was non-significantly greater in women carrying a female fetus compared to a male fetus, with mean decrease of 30.4 kU/L and 11.0 kU/L respectively ($p=0.32$).

Discussion

We found a consistent trend of higher maternal total IgE level during pregnancy in women carrying a male fetus as compared to a female fetus. Statistically significant differences according to offspring sex however were not reached. Total IgE levels decreased during pregnancy in all subjects, more so in women carrying a female fetus as compared to a male fetus.

Our results are consistent with findings in a previous study (11), where mothers of male offsprings had significantly higher levels of IgE measured in the post-partum period. To our knowledge, no other previous study has reported maternal IgE levels during pregnancy according to fetal sex.

The serum taken was stored at -20° centigrade from the time of the original study. Such storage has little influence on the ability to detect IgE (12), and a possible difference in deterioration of IgE in stored serum according to fetal sex is unlikely. The consistency in our findings supports this. Also we consider it unlikely that a possibly biased selection of study sample have influenced our results as the women were drawn randomly from a population study of almost 30,000 pregnant women.

A study by Schatz M., et al. (3) found that in the women whose asthma worsened during pregnancy, the 29th through to 36th weeks of gestation was a high-risk period.

If asthma exacerbations in pregnancy are mediated through IgE, a higher total IgE level in women carrying a female fetus should be expected, since asthma exacerbations in pregnancy is reported more often in women with a female fetus (1,2). Our results can not

confirm this and does, if anything, show a tendency in the opposite direction with a generally lower total IgE level during all three trimesters in women with a female fetus. Therefore IgE as a mediator of asthma seems not to be able to explain the worsening asthma course in women with a female offspring.

Defining reference values for total IgE levels in healthy, non-atopic adults have been subject to many studies, and normal values have ranged from 13 kU/L to 38kU/L (13-17). Our study findings show that pregnant women have elevated total IgE levels as compared to non-pregnant subjects. This finding suggests the increased total IgE level during pregnancy to be a general immunologic response to carrying a fetus. Also, our findings suggest that this response is elevated in women carrying a male fetus. This is supported by recent findings suggesting that male fetuses are subject to stronger intrauterine selection than female fetuses, with a higher risk of perinatal mortality, preterm delivery and late preeclampsia (18). Another explanation of higher mean total IgE levels in mothers of male fetuses could be that women giving birth to a male offspring have been shown to be more atopic than women giving birth to a female offspring (19), and atopic subjects are more likely to have elevated total IgE levels. Unfortunately no data on maternal atopic disease were available in our study.

In conclusion, maternal total IgE concentrations are increased in pregnancies with a male fetus as compared to a female fetus. The asthma exacerbations observed in asthmatic women carrying a female fetus may therefore not be entirely IgE mediated. The elevated total IgE levels in women carrying a male fetus may be an expression of an immunologic reaction to an opposite sex fetus.

Our results encourage further investigations to determine normal total IgE levels during pregnancy, and explanations for and possible implications of the observed difference in total IgE level in maternal blood according to fetal sex.

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Table 1: Maternal serum level of immunoglobulin E in pregnancy according to trimester and offspring sex in a random sample of 392 pregnant women.

	1 st trimester		2 nd trimester		3 rd trimester	
	Male (n=196)	Female (n=168)	Male (n=178)	Female (n=152)	Male (n=143)	Female (n=123)
Mean						
(kU/L)	101.2	92.5	73.2	67.6	89.2	68.5
Proportion						
>150 kU/L	15.8%	12.5%	14.6%	11.2%	14.0%	9.1%