Maternal Lipid Profile During Early Pregnancy and Pregnancy Complications and Outcomes: The ABCD Study

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Context: Elevated lipid levels during late pregnancy are associated with complications and adverse outcome for both mother and newborn. However, it is inconclusive whether a disturbed lipid profile during early pregnancy has similar negative associations.

Objective: Our objective was to investigate whether nonfasting maternal total cholesterol and triglyceride levels during early pregnancy are associated with six major adverse pregnancy outcomes.

Methods: Data were derived from the Amsterdam Born Children and Their Development (ABCD) cohort study. Random blood samples of nonfasting total cholesterol and triglyceride levels were determined during early gestation (median = 13, interquartile range = 12–14 wk). Outcome measures were pregnancy-induced hypertension (PIH), preeclampsia, preterm birth, small/large for gestational age (SGA/LGA), and child loss. Only nondiabetic women with singleton deliveries were included; the baseline sample consisted of 4008 women. Analysis for PIH and preeclampsia were performed in nulliparous women only (n = 2037).

Results: Mean (SD) triglyceride and total cholesterol levels were 1.33 (0.55) and 4.98 (0.87) mmol/liter, respectively. The incidence of pregnancy complications and perinatal outcomes were as follows: PIH, 4.9%; preeclampsia, 3.7%; preterm birth, 5.3%; SGA, 9.3%; LGA, 9.3%; and child loss, 1.4%. After adjustments, every unit increase in triglycerides was linearly associated with an increased risk of PIH (OR = 1.60, P = 0.021), preeclampsia (OR = 1.69, P = 0.018), LGA (OR = 1.48, P < 0.001), and induced preterm delivery (OR = 1.69, P = 0.006). No associations were found for SGA or child loss. Total cholesterol was not associated with any of the outcome measures.

Conclusions: Elevated maternal triglyceride levels measured during early pregnancy are associated with pregnancy complications and adverse pregnancy outcomes. These results suggest that future lifestyle programs in women of reproductive age with a focus on lowering triglyceride levels (i.e. diet, weight reduction, and physical activity) may help to prevent hypertensive complications during pregnancy and adverse birth outcomes.

Abbreviations: ABCD, Amsterdam Born Children and Their Development; BMI, body mass index; CI, confidence interval; LGA, large for gestational age; OR, odds ratio; PIH, pregnancy-induced hypertension; PRN, Dutch Perinatal Registration; PTB, preterm birth; SGA, small for gestational age; TC, total cholesterol, TG, triglycerides.
Adverse pregnancy outcomes have serious consequences (e.g., increased perinatal morbidity and mortality of mother and child) in the short term (1) and also increase the manifestation of disease later in life. For instance, preterm delivery and being born small for gestational age (SGA) or large for gestational age (LGA) are associated with increased risk for type 2 diabetes, cardiovascular diseases, and hypertension at adult age (2–4). Although obstetric care has improved, pregnancy complications and perinatal morbidity are still present in Western societies (5). Therefore, it is of clinical and economic importance to prevent adverse pregnancy outcomes by exploring causal factors for these outcomes.

One of the causal factors for perinatal morbidity and mortality could be the maternal atherogenic lipid profile early in pregnancy. During normal pregnancy, women show an increase in lipid levels, including levels of triglycerides (TG) and total cholesterol (TC) as gestational age progresses (6–9). Both TG and TC are taken up by the placenta and metabolized and transported to the fetus in various forms (10, 11); this shows that both lipids are essential for the development of the fetus. However, high levels of maternal TC and/or TG are associated with preterm birth (PTB) (1, 12–14), pregnancy-induced hypertension (PIH) (15, 16), preeclampsia (16–21), and LGA (22–24). Conversely, decreased levels of TC during pregnancy are associated with PTB (13) and an increased risk of the infant to be born SGA (1, 13, 25). However, there are reports of no association between maternal lipid profile and pregnancy outcome (26). To our knowledge, only one small study investigated TG and fetal mortality and found no association between them (27).

These conflicting results might (in part) be explained by differences in research design [e.g. case-control studies (12, 15, 16, 19) vs. cohort studies (13, 14, 17, 21), small sample size (16, 17, 21–23, 27), incomplete adjustment for confounders (13, 16, 23), or differences in study populations (15, 16, 21, 23, 26, 27). An important point of concern in earlier research is the sample time. So far, most studies focused on the lipid profile that is expressed during the second and third trimesters (13, 15, 16, 18, 22–25). In these cases, changes in lipid profile may be due to other factors, e.g. pregnancy-related complications and/or placenta dysfunction, and this may hinder interpretation in terms of cause or consequence.

Against this background, in a large cohort of pregnant women, we explored whether associations exist between maternal TC and TG levels during the first trimester and important adverse pregnancy outcomes, i.e. PIH, preeclampsia, PTB (spontaneous and induced), SGA, LGA, and child loss.

Subjects and Methods

This study is part of the Amsterdam Born Children and Their Development (ABCD) cohort study (www.abcd-studie.nl). The ABCD study is a prospective community-based cohort study that examines the association between maternal lifestyle; medical, psychosocial, and environmental conditions during pregnancy; and the child’s health at birth and in later life. Details of the ABCD study design have been described earlier (28–32). Approval of the study was obtained from the Central Committee on Research Involving Human Subjects in The Netherlands, the medical ethics review committees of the participating hospitals, and the Registration Committee of the Municipality of Amsterdam. All participants gave their written informed consent.

Study population

Between January 2003 and March 2004, all pregnant women living in Amsterdam were invited to participate in the ABCD study during their first prenatal visit to the obstetric care provider, around the 12th week of gestation. These women were requested to complete an extensive questionnaire about sociodemographic characteristics, obstetric history, lifestyle, and psychosocial conditions. The questionnaire was available in Dutch, English, Turkish, and Arabic. Of all 12,373 pregnant women who were invited, 8266 returned the questionnaire (67% response rate). These women were also asked to participate in the ABCD biomarker study. Therefore, additional blood sampling was taken during routine blood collection for screening purposes. The response rate was 53% (n = 4389), and TC and TG analyses were available for 4185 women. Information on pregnancy outcomes was obtained from the Youth Health Care Registration and the Dutch Perinatal Registration (PRN).

Women who had multiple gestation or who had no data on the gestational age at blood sampling, women with diabetes (pre-existent as well as pregnancy induced), and those using lipid-altering medication (e.g. antiepileptic drugs, steroids, insulin, antidepressants, thyroid hormones, or sleep medication) were excluded. The final sample included 4008 women (Fig. 1).

Biochemical analyses

A serum blood sample was taken to determine TC and TG levels. Nonfasting sampling was performed. The blood samples were taken in a 9-ml Vacuette (Greiner BV, Alphen aan de Rijn, The Netherlands) for the preparation of serum. At the Regional Laboratory for Health Protection Research Amsterdam, 1-ml aliquots were prepared by centrifugation (1600 × g for 10 min at room temperature) and stored at –80°C until analysis. The TC and TG levels in the serum were processed in the Laboratory for Toxicology, Pathology, and Genetics of the Dutch Institute for Public Health and the Environment. TC was assayed with the cholesterol oxidase-phenol aminophenazone method on a Hitachi 912 analyzer (Roche Diagnostics, Mannheim, Germany), and TG assay was performed using the glycerol-3-phosphatase oxidase-phenol aminophenazone method (Roche Diagnostics); the interassay coefficient of variation was 1.6% for TC and 2.1% for TG.

Maternal outcome

PIH was defined as a diastolic pressure of 90 mm Hg or higher after 20 wk gestation in a previously normotensive woman. Preeclampsia was defined by the combination of ges-
pertension in Pregnancy (33).

- Hypertension and proteinuria of at least 0.3 g/24 h or
dipstick at least 2+ after 20 wk gestation, according to the
guidelines of the International Society for the Study of Hyp-
ertension in Pregnancy (33).

Women with chronic hypertension (diastolic pressure ≥90
mm Hg or the necessity for antihypertensive treatment before
pregnancy or before 20 wk gestational age) who had diastolic
pressure of at least 90 mm Hg after 20 wk of gestation were
included in the superimposed PIH group or the preeclampsia
group if they also had proteinuria.

The association between maternal lipid profile and both PIH
and preeclampsia was evaluated only in nulliparous women who
gave informed consent to retrieve information from their medical
files (88%, n = 2037). The medical files of the nulliparous
women who documented elevated blood pressure in the ques-
tionnaire or who had a diastolic blood pressure of 90 mm Hg or
higher and/or proteinuria in the PRN were reviewed for confir-
mation of the diagnosis preeclampsia or PIH (29).

Perinatal outcome

The perinatal health outcomes explored were PTB, SGA, and
LGA. PTB was defined as a delivery between 24.0 and 36.6 wk
of completed gestation. Data on gestational duration were based
on ultrasound or, when unavailable (10%), from timing of the
last menstrual period. The PRN registered the onset of deliveries
(e.g. spontaneous, induction, and cesarean section). Based on
these data, we divided PTB into spontaneous and induced PTB
(30). Spontaneous PTB was defined as delivery onset by spon-
taneous preterm labor or premature rupture of membranes. In-
duced PTB was defined as delivery onset through induction or
primary cesarean section. Newborns were categorized as SGA
when they had a birth weight below the 10th percentile for ges-
tational age based on gender- and parity-specific standards from
the PRN (34). Infants were categorized as LGA when they had a
birth weight above the 90th percentile for gestational age based
on the same gender- and parity-specific standards from the PRN.
Child loss included miscarriages (<22 wk), fetal death (>22 wk
of gestation/delivery), and early neonatal death (0–7 d after de-
ivery). Nons spontaneous abortions (n = 7) and unknown child
losses (n = 64) were excluded, which resulted in 3944 women for
this outcome (31). For PTB, SGA, and LGA, only deliveries of 24
wk or later were included, which resulted in a total sample of
3912 for these outcomes.

Covariates

The following covariates were obtained from the question-
naire and included in the analysis: maternal age (years), parity (0,
≥1), maternal education (years of education after primary
school), ethnicity (based on country of birth of the pregnant
woman: Dutch, Turkish, Moroccan, Surinamese, or other), ma-
ternal prepregnancy body mass index (BMI, based on self-re-
ported height and weight), physical activity during the previous
week scored by calculating a metabolic equivalent score for the
various reported activities using the compendium of physical
activities (33), smoking during pregnancy (yes/no), and chronic
hypertension (yes/no). Missing data on prepregnancy weight
(8%) and maternal length (3%) were randomly imputed by mod-
els using linear regression analysis (36).

Statistical analysis

During pregnancy, the increase in lipid levels (6, 8), and there-
fore TG and TC levels, were corrected for gestational age at the
time of blood sampling. Descriptive statistics were used to profile
the sample by using ANOVA for continuous variables. To eval-
uate the association between maternal lipids and the perinatal
and maternal outcomes, multiple logistic regressions were per-
formed. First, unadjusted associations between continuous TC
and TG and the outcomes were explored, followed by multi-
variable analyses in which a priori stated confounders were
added to the model. Adjustments were made for maternal age,
parity, maternal education, ethnicity, prepregnancy BMI, physical
activity, smoking, and preexistent hypertension. Maternal
age, maternal education, prepregnancy BMI, and physical ac-
tivity were included as continuous variables. For the analysis
with SGA and LGA as the outcome variable, the variable parity
was not included in the multivariable model because the defini-
tions of SGA and LGA already accounted for parity. We also
excluded parity for PIH and preeclampsia analyses, because only
nulliparous women were involved. PIH analysis did not include
preeclampsia cases and vice versa. We explored whether there
were differences in associations by prepregnancy BMI status by
testing for an interaction between prepregnancy BMI and TC or
TG level in the multivariable models.

No departure from linearity was found on the log odds scale
between dichotomous outcomes and TG or TC. This was inves-
tigated using four splines and likelihood ratio tests (all P values
>0.52). The multivariable logistic models were used to estimate
the probability for adverse outcomes as a function of TG or TC.

In all analyses, a P value <0.05 was considered statistically
significant. The analyses were performed with SPSS package
version 16.0 (SPSS Inc., Chicago IL) and the statistical package R
2.13.1.

Results

Study population

The women in the present study had a mean (SD) age of
30.9 (4.9) yr; 56.4% were nulliparous, 20.7% were over-
pertension. Mean levels of TG were significantly higher in smoked during pregnancy, and women with chronic hy-
more often nulliparous (the included mothers were significantly older (n
1). Compared with mothers who completed the question-
aire but were not included in this study (no blood sample
weight or obese, and 67.7% were of Dutch origin (Table
1). Compared with mothers who completed the question-
aire but were not included in this study (no blood sample
characteristics of study participants according to maternal TC and TG levels
TABLE 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
<th>TG level ± SD (mmol/liter)</th>
<th>TC level ± SD (mmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>593 (14.8)</td>
<td>1.30 ± 0.54</td>
<td>4.83 ± 0.82</td>
</tr>
<tr>
<td>25–35 (reference)</td>
<td>2783 (69.4)</td>
<td>1.32 ± 0.54</td>
<td>5.01 ± 0.88</td>
</tr>
<tr>
<td>&gt;35</td>
<td>632 (15.8)</td>
<td>1.39 ± 0.56</td>
<td>5.02 ± 0.83</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2314 (57.7)</td>
<td>1.30 ± 0.50</td>
<td>5.02 ± 0.84</td>
</tr>
<tr>
<td>≥1</td>
<td>1694 (42.3)</td>
<td>1.37 ± 0.59</td>
<td>4.93 ± 0.90</td>
</tr>
<tr>
<td>Education (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>962 (24.2)</td>
<td>1.39 ± 0.61</td>
<td>4.94 ± 0.93</td>
</tr>
<tr>
<td>6–10 (reference)</td>
<td>1677 (42.2)</td>
<td>1.34 ± 0.56</td>
<td>5.00 ± 0.86</td>
</tr>
<tr>
<td>&gt;10 (reference)</td>
<td>1338 (33.6)</td>
<td>1.26 ± 0.46</td>
<td>5.00 ± 0.82</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch (reference)</td>
<td>2755 (68.7)</td>
<td>1.31 ± 0.53</td>
<td>5.01 ± 0.84</td>
</tr>
<tr>
<td>Turkish</td>
<td>128 (3.2)</td>
<td>1.53 ± 0.69</td>
<td>4.98 ± 0.94</td>
</tr>
<tr>
<td>Moroccan</td>
<td>204 (5.1)</td>
<td>1.36 ± 0.54</td>
<td>4.84 ± 0.88</td>
</tr>
<tr>
<td>Surinamese</td>
<td>177 (4.4)</td>
<td>1.40 ± 0.63</td>
<td>4.95 ± 0.89</td>
</tr>
<tr>
<td>Other</td>
<td>744 (18.6)</td>
<td>1.32 ± 0.56</td>
<td>4.93 ± 0.92</td>
</tr>
<tr>
<td>Prepregnancy BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>181 (4.5)</td>
<td>1.24 ± 0.44</td>
<td>4.82 ± 0.80</td>
</tr>
<tr>
<td>18.5–24.9 (reference)</td>
<td>2996 (74.8)</td>
<td>1.29 ± 0.53</td>
<td>4.96 ± 0.85</td>
</tr>
<tr>
<td>25–29.9</td>
<td>634 (15.8)</td>
<td>1.48 ± 0.59</td>
<td>5.10 ± 0.90</td>
</tr>
<tr>
<td>≥30</td>
<td>196 (4.9)</td>
<td>1.50 ± 0.59</td>
<td>5.09 ± 0.96</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exercise</td>
<td>975 (24.3)</td>
<td>1.35 ± 0.54</td>
<td>4.96 ± 0.87</td>
</tr>
<tr>
<td>Low (reference)</td>
<td>2290 (57.1)</td>
<td>1.34 ± 0.56</td>
<td>5.00 ± 0.88</td>
</tr>
<tr>
<td>Moderate</td>
<td>671 (16.7)</td>
<td>1.26 ± 0.51</td>
<td>4.98 ± 0.84</td>
</tr>
<tr>
<td>Vigorous</td>
<td>71 (1.8)</td>
<td>1.21 ± 0.44</td>
<td>4.86 ± 0.75</td>
</tr>
<tr>
<td>Smoking while pregnant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3521 (90.2)</td>
<td>1.31 ± 0.53</td>
<td>4.98 ± 0.86</td>
</tr>
<tr>
<td>Yes</td>
<td>381 (9.8)</td>
<td>1.49 ± 0.65</td>
<td>5.08 ± 0.93</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3841 (96.7)</td>
<td>1.32 ± 0.54</td>
<td>4.98 ± 0.86</td>
</tr>
<tr>
<td>Yes</td>
<td>132 (3.3)</td>
<td>1.44 ± 0.61</td>
<td>5.04 ± 0.98</td>
</tr>
</tbody>
</table>

TG and TC levels were standardized at median gestational age at blood sampling (13 wk).

a P < 0.05.

b P < 0.01.

c P < 0.001.

weight or obese, and 67.7% were of Dutch origin (Table
those with PIH or preeclampsia and those who gave birth
to LGA babies (Table 2).

Maternal outcomes

Of the nulliparous women, 4.9% developed PIH (not complicated by proteinuria) and 3.7% preeclampsia (Table
3). We observed a positive linear relationship between
to TG levels and the risk for subsequent PIH and preeclampsia (Fig. 2). Univariate analysis showed that a 1-U increase
in TG was associated with an increased risk of PIH [odds ratio (OR) = 1.24, 95% confidence interval (CI) = 1.21–
2.43] and preeclampsia (OR = 1.85, 95% CI = 1.24–
2.77; Table 3). This association was only slightly reduced
after adjustment for confounders (PIH: OR = 1.60, 95% CI = 1.10–2.32; preeclampsia: OR = 1.69, 95% CI = 1.10–2.60). Translating these numbers to an absolute probability, TG levels of 0.60 mmol/liter (2.5th percentile)
means an expected risk for PIH of 3.7% (95% CI = 2.5–
Results are shown as mean ± SD. TG and TC levels were standardized at median gestational age at blood sampling (13 wk). Preeclampsia cases were excluded from the analysis of PIH. Only primiparae were included for the analysis of PIH and preeclampsia. PIH cases were excluded from the analysis of preeclampsia. Only pregnancies with gestational age of at least 24 wk were included in preterm delivery and LGA/SGA analysis.

a P < 0.05.

b P < 0.01.

c P < 0.001.

5.5), whereas TG levels of 2.67 mmol/liter (97.5th percentile) increase this risk to 8.9% (95% CI = 5.3–14.5), a more than 2-fold enhancement. In case of preeclampsia, expected risk increases from 2.4% (95% CI = 1.5–3.8) to 7% (95% CI = 3.7–12.0) with TG levels at the 2.5th percentile and 97.5th percentile, respectively (Fig. 2). TC was not associated with PIH or preeclampsia (Table 3). Associations did not differ according to prepregnancy BMI status (P values for interaction ranged from 0.47–0.92).

Perinatal outcomes

The prevalence of PTB was 5.3%, for SGA 9.3%, for LGA 9.3%, and for child loss 1.4% (Table 3). TG levels were not associated with total PTB, SGA, and child loss (Table 3). However, when dividing PTB into induced (prevalence 1.5%), spontaneous (3.6%), and unknown subtype (0.2%), a significant positive association was found between TG levels and induced PTB (adjusted OR = 1.69, 95% CI = 1.16–2.45) but not for spontaneous PTB (adjusted OR = 0.87, 95% CI = 0.62–1.23). Of all induced PTB, 57.1% were complicated by preeclampsia and 3.4% by PIH. Univariate logistic regression analyses showed that a 1-U increase in TG levels was associated with an increased risk for LGA (OR = 1.44, 95% CI = 1.20–1.71). After adjustment for confounders, TG remained significantly associated with increased risk for LGA (OR = 1.48, 95% CI = 1.23–1.78). Translating these numbers to an absolute probability, TG levels of 0.60 mmol/liter (2.5th percentile) means an expected risk for LGA of 7.5% (95% CI = 6.0–8.8), which increases to 15% (95% CI = 11.8–19.0) in those with a TG level of 2.65 mmol/liter (97.5th percentile; Fig. 2).

TC showed no association with pregnancy outcome (Table 3). Associations did not differ according to prepregnancy BMI status (P values for interaction ranged from 0.47–0.95).

### TABLE 2. Mean TG and TC levels by maternal and perinatal outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TG level (mmol/liter)</th>
<th>TC level (mmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Cases</td>
</tr>
<tr>
<td>PIH (n = 1962)</td>
<td>1.29 ± 0.49</td>
<td>1.44 ± 0.60</td>
</tr>
<tr>
<td>Preeclampsia (n = 1938)</td>
<td>1.29 ± 0.49</td>
<td>1.50 ± 0.59</td>
</tr>
<tr>
<td>Preterm delivery (n = 3912)</td>
<td>1.33 ± 0.55</td>
<td>1.36 ± 0.55</td>
</tr>
<tr>
<td>SGA (n = 3912)</td>
<td>1.33 ± 0.54</td>
<td>1.35 ± 0.61</td>
</tr>
<tr>
<td>LGA (n = 3912)</td>
<td>1.32 ± 0.54</td>
<td>1.44 ± 0.61</td>
</tr>
<tr>
<td>Child loss (n = 3944)</td>
<td>1.33 ± 0.55</td>
<td>1.27 ± 0.49</td>
</tr>
</tbody>
</table>

The crude model was standardized at median gestational age at blood sampling (13 wk). Model 1 is the crude model plus adjustment for maternal age, ethnicity, parity, prepregnancy BMI, maternal education level, physical activity, smoking during pregnancy, and chronic hypertension. Preeclampsia cases were excluded from the analysis of PIH. Only primiparae were included for the analysis of PIH and preeclampsia. PIH cases were excluded from the analysis of preeclampsia. Only pregnancies with gestational age of at least 24 wk were included in preterm delivery and LGA (>90th percentile) and SGA (<10th percentile) analysis. SGA/LGA analysis did not include parity because by definition this information is included.

a P < 0.05.

b P < 0.01.

c P < 0.001.
Discussion

In this large community-based cohort study it was found that plasma TG levels, but not TC levels, in the first term of pregnancy were independently and positively associated with adverse pregnancy outcomes for both mother (PIH and preeclampsia) and newborn (LGA). A pronounced lipid profile (including TC and TG levels) in the last term of pregnancy is positively associated with adverse pregnancy outcomes. Indeed, the risk for PIH (not complicated by proteinuria) and preeclampsia is reported to be increased with increased lipid levels measured in late pregnancy (15, 16); however, similar results were reported in studies in which a lipid profile was determined in early pregnancy (19, 21) or even 4 yr before pregnancy (17). Although the preeclampsia incidence was comparable (3.7%), these differences might be explained by the fact that our sample comprises a relatively healthy population (diabetic patients were excluded from our analysis) with lower prevalence rates in prepregnancy overweight/obesity: 20.7% compared with the other two studies (>30%).

No association was found between TG levels and total preterm birth, although we did observe a significant association between mother’s TG levels and induced PTB. These findings might be explained by the large proportion of women undergoing an induced PTB after they had suffered from preeclampsia. To our knowledge, no other study has separated total PTB into its subtypes; therefore,
we cannot compare our results with respect to induced preterm delivery. Magnussen et al. (14) concluded that the association found between high TG and TC before pregnancy and PTB could partly be explained by hypertensive disorders in pregnancy. In a case-control study, Catov et al. (12) included only spontaneous PTB and found an association between high TC (>6.0 mmol/liter) or TG levels (>3.6 mmol/liter) and very early PTB (before wk 34 of gestation). After similar adjustments, we were unable to confirm these latter results (data not shown). Their range in TC levels were comparable to ours; however, the TG levels were much higher compared with our range of TG levels (95% of our population had levels between 0.60 and 2.67 mmol/liter). This could explain why we found no association between spontaneous PTB and maternal lipid levels.

Our results are in line with others reporting a positive association between TG levels and LGA but not between TC levels and LGA (22–24). Edison et al. (13) reported that TC levels of less than the population 3rd percentile (<4.0 mmol/liter at wk 17 of gestation) were associated with SGA. The fact that their TC level was significantly lower than ours could explain this incongruent result. Subsequently, it might be postulated that only maternal TC levels in the lowest range will be related to serious fetal growth restriction. Previous results of our cohort showed a borderline significant association between low TC and increased risk for SGA (32). We hypothesize that lower TC levels in our relatively healthy cohort was associated with only small changes in birth weight that do not translate to more severe measures of growth retardation.

Our results show no effect of TG or TC on child loss (including miscarriages and perinatal deaths), which is consistent with another study examining perinatal death (27). However, the numbers of child losses in our sample were too small to perform separate analyses for subtypes of child loss; moreover, the data on miscarriages were probably incomplete. More research in larger cohorts is needed to allow us to draw valid conclusions.

The observation that TG levels measured in the first trimester are associated with complications in pregnancy for both mother and child is intriguing. In fact, most reports mainly focused on maternal lipid profiles in late pregnancy, stating that circulating lipids exert a direct harmful effect on the endothelium of placental vasculature. Increasing evidence suggests that elevated plasma lipids, including TG or its related remnants, may induce endothelial dysfunction (37, 38). Increased peroxidation of these elevated plasma lipids causes enhanced oxidative stress by progressively producing free radicals and lipid peroxides (21). Lipid peroxides are toxic compounds that have the potential to damage endothelial cells (16). Endothelial dysfunction in placenta is reported to be associated with maternal complications and newborn’s growth retardation. Our observations may indicate that additional mechanisms (such as placenta vasculature) are in development at the end of the first trimester. During placenta development, local angiogenesis is influenced by various factors, such as distinctive fatty acids. In parallel, higher TG levels give an increase in circulating free fatty acids. Depending on dietary composition, molecular lipid species will be incorporated in the TG particle displaying different capacity with regard to endothelial toxicity (e.g. oxidizability). Moreover, free fatty acids levels could act as growth factors, and high levels of free fatty acids are known to compete for hormones bound to albumin (e.g. sex hormones) with a subsequent increase in free hormone levels, giving them a role in placenta capacity and intrauterine growth and development (39, 40). Subsequently, our observation may have generated a hypothesis that TG levels and their related factors could be one of the contributors that affect vascular development of the early placenta. The increase in absolute risk from 2.5–97.5th percentile in maternal TG levels is about 10%, and therefore, TG may be considered as a modest contributing factor.

The major strengths of the present study include the large sample size and the community-based sample; however, there are some limitations. Selective participation may have occurred with a predominant inclusion of healthy females. In line with these remarks, we excluded the participation of women suffering from prepregnancy and gestational diabetes and women using lipid-lowering therapy. Despite this selection, our approach was similar to other cohort studies (17, 21). On the other hand, having a disturbed glucose metabolism increases the risk of most negative obstetric and perinatal outcomes (41). If we had not excluded women with diabetes, the associations found in the current analysis might have been more pronounced. Some of our confounders, especially a high BMI, could (in part) be in the causal path of higher lipid levels (42) with a subsequent risk of overcorrection. When we analyzed the multivariate model without prepregnancy BMI as a confounder, there was a lower reduction, or even a rise, in the corrected OR of the measured outcomes. This could mean that the risk of an adverse event is probably higher than found in our models.

The venous blood sampling occurred in a nonfasting state on one occasion only; we assumed that this may have only slightly diluted our results. Our results are in accordance with other studies that used nonfasting (17–19, 21) and fasting (22) lipid levels. Furthermore, lifestyle and clinical characteristics were self-reported, which may have led to bias for some measures, because women could misreport, e.g. their weight and height (43); however, because
of our large sample, we think this would have minor influence on our results, although we cannot rule out some residual confounding. We were not able to adjust for weight gain during pregnancy and dietary intake, two factors that could confound our results. For preeclampsia and PIH, we included only nulliparous women, which reduced our sample size. In our cohort, only medical files of nulliparous women with documented elevated blood pressure, diastolic blood pressure of at least 90 mm Hg, and/or proteinuria were reviewed for confirmation of the diagnosis for preeclampsia or PIH. This was done for nulliparous women only, because their risk for preeclampsia is higher. Although this implies that our prevalence is higher compared with the general pregnant population, this probably had no influence on our results with respect to TG. Our sample size remains similar in size to (or larger than) other studies with respect to preeclampsia and PIH (16, 18, 19, 21).

In conclusion, our results suggest that elevated maternal TG levels in the first trimester of pregnancy are a significant, but modest, contributor in the expression of PIH, preeclampsia, induced preterm birth, and children to be born LGA. With this observation, inclusion of a lipid profile may be considered early in pregnancy or perhaps even in the preconception screening. Additional studies are needed to evaluate whether lowering TG levels by means of lifestyle programs (e.g. diet and physical activity) is beneficial in reducing adverse pregnancy outcome.

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