Normalizing Metabolism in Diabetic Pregnancy: Is It Time to Target Lipids?

Helen L. Barrett,[1,2,3] Marloes Dekker Nitert,[1,3] H. David McIntyre,[3,4] and Leonie K. Callaway[2,3]

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REVIEW ARTICLE

Outcomes in pregnancies complicated by preexisting diabetes (type 1 and type 2) and gestational diabetes mellitus have improved, but there is still excess morbidity compared with normal pregnancy. Management strategies appropriately focus on maternal glycemia, which demonstrably improves pregnancy outcomes for mother and infant. However, we may be reaching the boundaries of obtainable glycemic control for many women. It has been acknowledged that maternal lipids are important in pregnancies complicated by diabetes. Elevated maternal lipids are associated with preeclampsia, preterm delivery, and large-for-gestational-age infants. Despite this understanding, assessment of management strategies targeting maternal lipids has been neglected to date. Consideration needs to be given to whether normalizing maternal lipids would further improve pregnancy outcomes. This review examines the dyslipidemia associated with pregnancy complicated by diabetes, reviews possible therapies, and considers whether it is time to start actively managing this aspect of maternal metabolism.

Although rates of adverse outcomes in pregnancies complicated by preexisting diabetes (type 1 and type 2) and gestational diabetes mellitus (GDM) have improved, there is still excess maternal and fetal morbidity compared with normal pregnancy. Current management strategies focus on maternal glycemic control, which demonstrably improves pregnancy outcomes for mother and infant. Truly "normal" glucose levels in pregnancy appear lower than previously thought (1) and achieving currently recommended glucose targets in pregnancy carries a risk of hypoglycemia (2). The challenges in reaching glycemic targets before and after conception raise the question of whether other aspects of maternal metabolism could potentially be addressed to provide benefit to mother and infant.

Multiple maternal metabolic, hormonal, and inflammatory factors other than maternal glucose are associated with maternal and fetal outcomes and are altered in pregnancies complicated by prepregnancy diabetes and GDM. These include maternal amino acids, glycerol, ketones, and lipids (3). Lipid management in diabetes is acknowledged as a key therapeutic target in the nonpregnant setting. However, it has not been accorded the same attention in pregnancy. Abnormal maternal lipids in pregnancy have been associated with preeclampsia (4,5), preterm delivery (6), and large-for-gestational-age (LGA) infants (7). This review examines the dyslipidemia associated with pregnancy complicated by diabetes, reviews possible therapies, and considers whether there is sufficient evidence to start actively managing lipids in pregnancy.

LIPID METABOLISM IN PREGNANCY

Maternal metabolism is designed to provide adequate nutrition for fetal growth, in the form of glucose, ketones, lipids, and other fuels. In early pregnancy, maternal

[1]*UQ Centre for Clinical Research, The University of Queensland, Herston, Queensland, Australia*
[2]*Obstetric Medicine, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia*
[3]*School of Medicine, The University of Queensland, St. Lucia, Queensland, Australia*
[4]*Mater Medical Research Institute, Queensland, Australia*

Corresponding author: Helen L. Barrett, h.barrett@uq.edu.au.

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metabolism is anabolic, which, combined with pregnancy-related hyperphagia, results in increased maternal fat stores. In the third trimester, maternal metabolism becomes more catabolic to support the acceleration of fetal growth (3). Increased maternal insulin resistance combined with peripheral adipose tissue lipolysis results in increased maternal lipoprotein concentrations and elevated lipoprotein triglyceride content, including VLDL, HDL, and LDL (Table 1). There is concomitantly increased maternal hepatic gluconeogenesis and preferential maternal utilization of ketones in the fasting state, freeing maternal glucose for use as the primary substrate for fetal energy production (3) (Fig. 1).

Provision of free fatty acids, as well as the fatty acids and cholesterol transported in maternal lipoproteins, is important for fetal growth and development (3). Maternal lipoproteins do not pass directly across the placenta, but their constituents are able to be transported to the fetus via interactions with specific lipoprotein receptors, lipases, and fatty acid–binding transport proteins on the placenta, allowing placental uptake of triglycerides and cholesterol and passage to the fetus (8) (Fig. 2). Additionally, direct uptake of chylomicron remnant particles has been demonstrated in mouse placenta, raising the possibility that this may also occur in human pregnancy (9). Changes in placental processing of lipids in the setting of diabetes have been expertly reviewed by Herrera and Ortega-Senovilla (3) and Desoye et al. (8).

MATERNAL LIPIDS IN DIABETIC PREGNANCY

Many, but not all, studies examining lipids in women with preexisting diabetes or GDM in pregnancy report a deviation from the usual patterns of pregnancy-associated changes in maternal lipids. Changes in maternal lipoproteins or differences in the triglyceride, cholesterol, or apolipoprotein content of the maternal lipoproteins have been reported in pregnancies complicated by diabetes (Supplementary Table 1).

Preexisting Type 1 Diabetes

The most common finding in studies examining pregnant women with well-controlled type 1 diabetes is that the changes in lipoproteins are similar to women with uncomplicated pregnancy. However, the coexistence of other maternal factors, including maternal obesity, preexisting metabolic syndrome, poor glycemic control, renal disease, and the development of preeclampsia, has been associated with an exaggeration of the gestational change in maternal lipoproteins. Women with type 1 diabetes and coexistent metabolic syndrome have lower HDL cholesterol (HDL-C) and higher triglycerides in the first trimester, and although both women with and without metabolic syndrome showed an increase in cholesterol, HDL-C, LDL cholesterol (LDL-C), and triglycerides from the first to third trimester, the increase (in all except HDL-C) was nonsignificant in women with preexisting metabolic syndrome (10). Women with type 1 diabetes and renal disease (as defined by the presence of $>$0.05 g protein/24 h in urine) showed a greater increase in cholesterol and LDL-C but not triglycerides across gestation than those with no renal disease (11). Women with well-controlled type 1 diabetes (mean HbA_{1c} 6.1%, 43 mmol/mol) had lipoprotein levels comparable to women with uncomplicated pregnancy, but those with poor control (HbA_{1c} 8.3%, 67 mmol/mol) at the time of delivery had higher triglycerides and VLDL and lower HDL_3 levels (12). Women with type 1 diabetes who go on to develop preeclampsia later in pregnancy have higher LDL-C and cholesterol than women with type 1 diabetes who do not develop preeclampsia (13).

Preexisting Type 2 Diabetes

Data on lipids in women with type 2 diabetes in pregnancy are scarce. Studies have shown higher free fatty acid levels compared with normal pregnancy (14) and higher triglyceride and lower HDL-C levels in the first trimester when compared with women with type 1 diabetes in pregnancy (15), or no difference in any lipoprotein compared with either type 1 diabetes or GDM (16). However, $<$80 women with type 2 diabetes were included in these reports.

GDM

In women with GDM, maternal triglycerides have been reported to be increased in all trimesters of pregnancy (17), although this is not a universal finding. Similarly, maternal cholesterol has been reported as increased (17) or unchanged (14,18,19) across gestation. Studies in women with GDM have shown no difference (18) or a decline in LDL-C concentration (20) but with increased levels of small, dense LDL (18,20) and increased LDL oxidation (17).

Maternal Obesity

Maternal obesity is associated with a range of adverse outcomes for mother and infant, including higher rates of preeclampsia, GDM, and macrosomia. Maternal obesity is associated with an increase in maternal lipid levels, higher triglycerides and VLDL (21), and lower HDL-C (21) than observed in lean women. Obese women without GDM have been shown to have higher glucose profiles on continuous glucose monitoring performed during pregnancy than normal-weight women; the mean time spent with glucose $>$6.7 mmol/L is longer in obese than normal-weight women (209 $\pm$ 62 min vs. 33 $\pm$ 12 min, $P = 0.001$) (22). In addition to changes in lipid and glucose metabolism, there is greater inflammation and more vascular endothelial dysfunction associated with obese pregnancy. Disentangling the effect of maternal obesity per se from that of maternal diabetes on maternal metabolism and pregnancy outcomes in the women with obesity and diabetes in pregnancy is almost impossible without very large cohorts with refined metabolic measures.

Table 1—Lipoprotein concentrations across gestation in normal pregnancy*

Trimester	Triglycerides (mmol/L)	Total cholesterol (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)
First	1.19 (0.80–1.23) [561]	4.56 (4.30–4.58) [561]	2.30 (2.30–2.33) [516]	1.68 (1.68–1.74) [516]
Second	1.80 (1.20–2.20) [1,076]	5.67 (5.00–6.29) [1,076]	2.95 (2.95–3.37) [1,031]	1.79 (1.76–2.15) [1,031]
Third	2.40 (1.76–2.84) [824]	6.66 (5.91–7.02) [824]	3.96 (3.32–4.07) [399]	1.97 (1.68–2.09) [399]

*Data are in mmol/L and represent weighted mean (range of means) [*n*] (6,15,17,18,23,30,61–63).

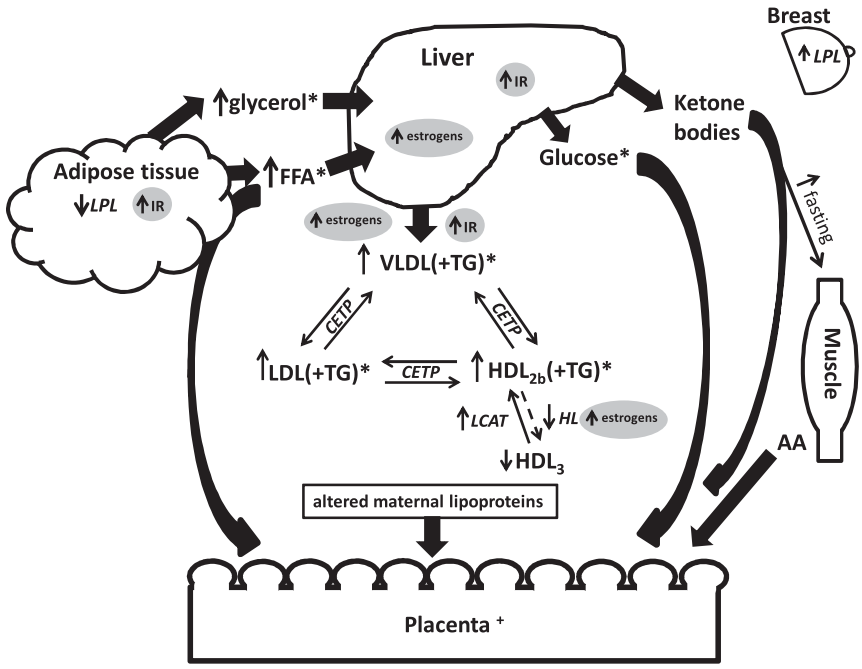

Figure 1—Maternal lipoprotein metabolism in late pregnancy. In the last trimester, elevated maternal insulin resistance and estrogen levels produce multiple changes in lipoprotein metabolism. These include a reduction of LPL activity in adipose tissue and serum, a reduction in hepatic lipase (HL), and an enhancement of the activity of cholesterol ester transfer protein (CETP). These alterations result in increased adipose tissue lipolysis, increasing the release of free fatty acids (FFAs) and glycerol from adipose tissue and their transfer to the liver and placenta. These substrates are used in the liver for gluconeogenesis, VLDL production, and ketone body synthesis and by the placenta. The VLDL produced in the liver has a higher triglyceride concentration than in the nonpregnant population. CETP activity transfers triglycerides from VLDL to LDL and HDL. HDL_{2b} increases more than the other HDL subfractions, due to a decrease in hepatic lipase activity and increased lecithin-cholesterol acyltransferase (LCAT) activity. In the fasting state, hepatic gluconeogenesis and hepatic β-oxidation are greatly increased, resulting in ketone body synthesis, providing potential alternative maternal fuel supplies and maintaining other substrate loads for fetal utilization. The mammary gland has increased LPL activity in late gestation and lactation. FFAs, cholesterol, glucose, ketone bodies, and amino acids can all be metabolized in the placenta. *Exaggerated in diabetic pregnancy. +See Fig. 2. This figure has been based in part on Herrera and Ortega-Senovilla (3). AA, amino acid; IR, insulin resistance; TG, triglyceride.

RELATION BETWEEN LIPIDS AND PREGNANCY OUTCOMES

Maternal Lipids Are Associated With Adverse Pregnancy Outcomes

In observational studies and larger population cohort studies in normal pregnancy, increasing maternal triglycerides in early pregnancy have been associated with increased rates of preeclampsia (4,5), future diagnosis of GDM (17,23), induced preterm delivery (5), and LGA infants (5). Low maternal HDL-C in early pregnancy has also been associated with increased risk of later GDM (23), and elevated HDL-C has been associated with lower rates of preterm birth (24). Both low (<10th centile) and high (>90th centile) maternal total cholesterol have been associated with preterm birth (6,25), with one study showing a trend to increased rates of microcephaly for low (<10th centile) maternal cholesterol (25) (Table 2). Overall, there is good evidence that elevated triglycerides and low levels of HDL-C are associated with adverse maternal and neonatal outcomes for women without diabetes.

Women with preexisting diabetes and GDM are at higher risk of developing preeclampsia than those with uncomplicated pregnancy. This risk is related to the degree of glycemic control. There is also some evidence of an association with maternal lipids. In women with type 1 diabetes, early pregnancy LDL-C was elevated in those who later developed preeclampsia (13). Conversely, in 184 women with GDM, maternal plasma cholesterol, LDL-C, HDL-C, and triglycerides did not differ in those who went on to develop preeclampsia (26). There are no studies examining the relationship between lipids and preeclampsia in women with type 2 diabetes. The association between lipids and preeclampsia is clearer in women with uncomplicated pregnancy than it is in women with diabetes in pregnancy.

Women with preexisting diabetes (27) or GDM are more likely to have infants born LGA than women with uncomplicated pregnancy even when maternal glucose control is considered "good" (mean fasting glucose 4.6 mmol/L and mean postprandial glucose 6.1 mmol/L close to term [28]). Infants born LGA have an increased fat mass (29). This trend has been associated with elevated maternal glucose levels and also maternal lipids. In women with preexisting diabetes, elevated maternal triglycerides and low HDL-C in the third trimester are associated with an increased risk of LGA infants (15). In GDM, maternal triglyceride levels measured post–oral glucose tolerance testing correlate with birth weight to the same extent as 1- and 2-h glucose measures (30). Further, in women with good glycemic control, maternal fasting free fatty acids and triglycerides at oral glucose tolerance test and delivery are independently related to the rate of LGA (7,28). In summary, babies born to women with preexisting or GDM are

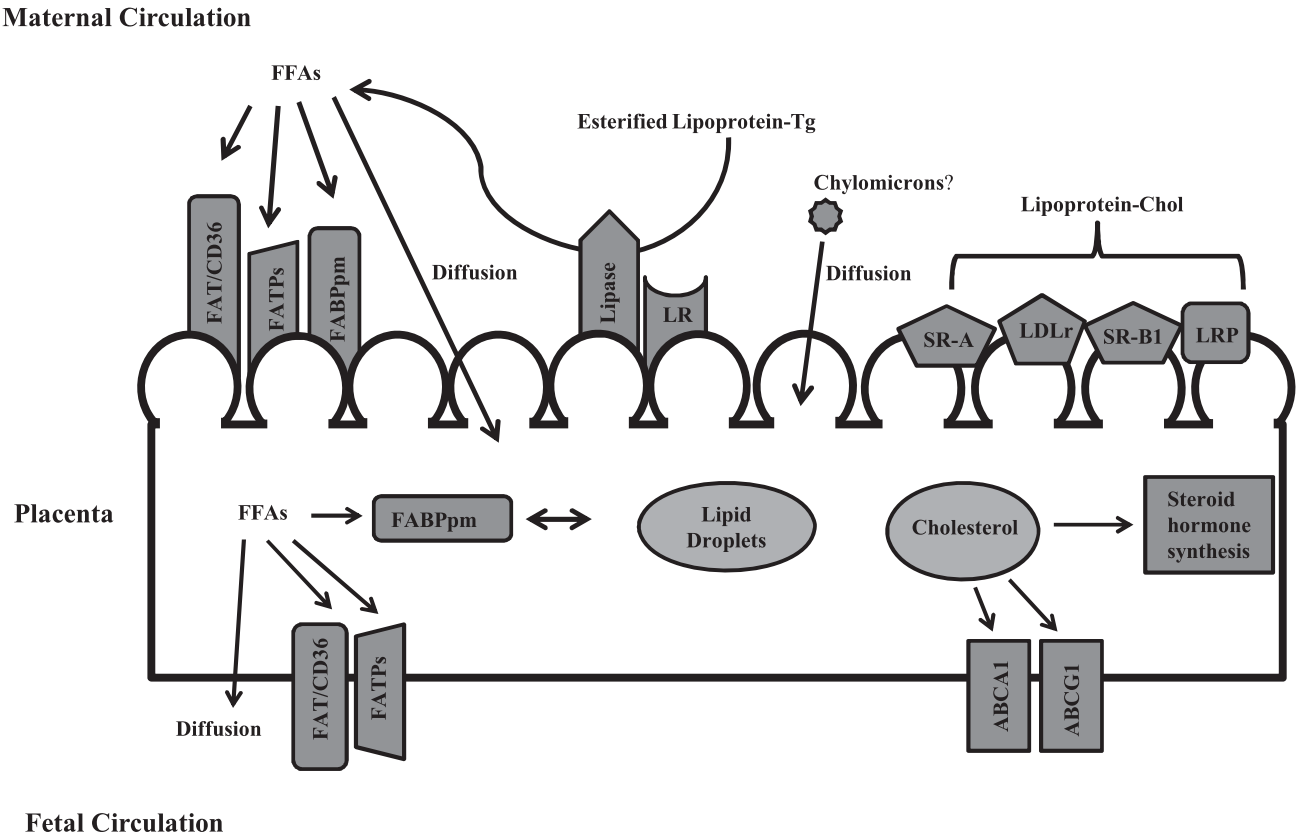

Figure 2—Proposed mechanisms involved in fatty acid and cholesterol transfer across the placenta. Maternal free fatty acids (FFAs) can be directly taken up into the trophoblast. Lipases, in particular endothelial lipase and LPL, release FFA from the maternal circulating lipoproteins (58). The placenta also takes up cholesterol. This is used in placental steroid hormone synthesis as well as transported to the fetus. The trophoblast expresses receptors for VLDL cholesterol (VLDL receptor), LDL-C (LDL receptor), and HDL-C (scavenger receptor class B type 1 [SR-B1]). After uptake, the cholesterol ester is hydrolyzed by the lysosome/endosome pathway (59). The mechanisms for release of FFAs and cholesterol from the fetal side of the syncytiotrophoblast and fetal endothelial cells are less well defined than those for uptake from the maternal side. FFAs move to the fetal circulation by facilitated diffusion or using fatty acid translocase (FAT/CD36) and fatty acid transport protein (FATP) in the syncytiotrophoblast basal membrane. Cholesterol is moved out of the trophoblast by secretion of lipoproteins, through complex formation with apoE, and efflux by SR-B1, ABCA1, and ABCG1 (59). Direct uptake of chylomicron remnant particles has been demonstrated in mouse placenta, raising the possibility that this may also occur in human pregnancy (9). This figure has been adapted from references 3,8,9,58–60. FABPpm, plasma membrane fatty acid binding protein; LR, lipoprotein receptor; LRP, lipoprotein-related protein; SR-A, scavenger receptor A.

more likely to be born large and to have higher adiposity, even in the setting of a normal body weight. Both of these have been associated with elevated maternal lipids.

Maternal lipids are abnormal in pregnancies complicated by diabetes, and these lipid abnormalities are associated with poorer maternal and infant health. Given that there is a persistent excess of pregnancy complications associated with diabetes, the addition of strategies to target maternal lipids may offer a way of normalizing another aspect of maternal metabolism in pregnancies complicated by diabetes. This may result in improved pregnancy outcomes.

Examination and comparison of the changes in maternal lipids in the setting of different maternal conditions and their relationship with pregnancy outcomes is complicated by the variation in gestational length at the time of measurement of maternal lipids. Studies also vary in whether fasting or nonfasting maternal blood samples were assessed. Other confounding factors include the degree of maternal glycemic control, the diagnostic criteria used for GDM, and the presence of maternal obesity.

One other aspect of maternal lipid metabolism in pregnancy that needs further exploration is the role of ethnicity. Ethnic differences in lipids have been described both in the nonpregnant (31) and the pregnant state (32), and the relationship between maternal lipids and pregnancy outcomes has been shown to vary between ethnicities (33). It is therefore difficult to compare directly between studies, even in women with the same underlying medical condition, and a more reliable comparison can only be made between groups within the same study under similar sampling conditions (Supplementary Table 1).

POSSIBLE THERAPEUTIC OPTIONS

To date, there are few randomized controlled trials specifically targeting the management of maternal lipids in pregnancy. Our considerations of possible approaches to lipid management in pregnancy are predominantly informed by the management of women with severe lipid abnormalities, such as in familial hyperlipidemic syndromes. Here we will examine the range of lifestyle and pharmacological strategies that could be considered in managing lipids in pregnancy.

Table 2—Maternal and fetal complications and the typical maternal lipid abnormalities preceding each

	Pregnancy not complicated by diabetes	GDM	Preexisting diabetes
Maternal complications			
Development of GDM	↑ triglycerides, ↑ cholesterol, ↑ LDL-C, ↓ HDL-C from early pregnancy (17,23)	↑ triglycerides, ↓ LDL-C, ↑ free fatty acids, ↑ HDL and VLDL triglyceride content, ↓ HDL-C at diagnosis (63–65), ↓ LDL particle size (20), unchanged lipoprotein concentration (18,19,62)	—
Development of preeclampsia	↑ triglycerides, in early pregnancy (4,5)	No difference in lipoproteins at diagnosis of GDM between those who did and did not go on to develop preeclampsia (26)	↑ LDL-C, ↑ large LDL, ↑ serum ApoB and ↑ ApoB-ApoAI ratio prior to the third trimester (13)
Infant complications			
Increased rates of preterm delivery	↑triglycerides, both ↓ (<10th centile) and ↑ (>90th centile) total cholesterol, ↑ non–HDL-C (5) (24)* (25)** (6)***	—	—
Lower rates of preterm delivery	↑ HDL-C in the second trimester (24)*	—	—
Microcephaly	↓ (<10th centile) maternal cholesterol (25)**	—	—
LGA infants/increased body fat %	↑ triglycerides, ↓ HDL-C, ↑ free fatty acid levels (5)	↑ triglycerides, ↑ free fatty acids correlated positively with fetal abdominal circumference, infant birth weight, and infant fat mass (28); in women with impaired glucose tolerance, incidence of LGA infants increased in those with triglycerides >75th centile (30); ↑ triglycerides in mothers of LGA infants (7)	↑ triglycerides, ↓ HDL-C associated with large infants (15)

This table shows alterations in lipid parameters during the pregnancy, preceding (not at the time of) the given outcome. *This study included 49 women with either GDM or preexisting diabetes in a total cohort of 651. The authors repeated analyses excluding these women and found the same results. **It is unclear whether this study included women with GDM and/or type 2 diabetes but it specifically excluded women with type 1 diabetes. ***Excluded preexisting diabetes.

Familial Hypertriglyceridemia Illustrates Possible Treatment Options

Severe maternal hypertriglyceridemia offers insight into the therapies that are potentially useful for maternal hyperlipidemia during pregnancy. Women with familial hypertriglyceridemia typically show levels of triglycerides >10 mmol/L (frequently much higher) and require active treatment during pregnancy to reduce their risk of pancreatitis, which is associated with adverse outcomes for mother and infant, including death (34). Most information about familial lipid syndromes in pregnant women currently comes from clinical case reports. However, examinations of the maternal, fetal, and placental physiology of familial lipid syndromes can potentially illuminate the processes in normal pregnancy. For example, studies of gene polymorphisms in lipoprotein lipase (LPL) highlight the bidirectional nature of the maternal-fetal relationship. If the fetus, but not the mother, carried the LPL gain-of-function mutation, LPL*S447×, maternal triglycerides, LDL-C, and apolipoprotein B (apoB) were lower but maternal HDL-C and apoA-I were higher. Conversely, if both fetus and mother carried the LPL*S447× mutation, neonatal lipid cord blood levels of lipids were decreased but maternal lipids were unchanged. If the fetus carried the loss-of-function LPL*N291S mutation, maternal triglycerides were increased instead (35). Examination of the basic physiology as well as placental nutrient transfer in women with familial hyperlipidemic syndromes could be extremely valuable in helping us decipher the importance of lipid physiology in maternal diabetes.

Management of severe hypertriglyceridemia in pregnancy has recently been reviewed by Goldberg and Hegele (34) and includes a very low-fat diet, omega-3 fatty acids, fibrates, niacin, and dextrose/insulin infusion combined with fasting and plasma exchange. Some of these therapies are unsuitable for use in a broader obstetric population. However, potential therapeutic options for less severe elevations of triglycerides would include omega-3 fatty acids, statins, niacin,

and fibrates, in addition to medications already used for treatment of diabetes in pregnancy, including diet, metformin, and insulin, which also influence maternal lipids. These therapies all have multiple effects on lipids, and some have additional anti-inflammatory, antithrombotic, or antioxidant effects.

Diet and Exercise

Diet and exercise are routinely advocated for management of hyperlipidemia for nonpregnant patients. In the literature examining the nonpregnant population, a Cochrane review of any dietary therapy for at least 3 months, aimed at reducing cardiac disease and excluding trials to reduce weight, found no difference in triglyceride levels but a small reduction in total cholesterol (0.15 mmol/L) and LDL-C (0.16 mmol/L) (36). Trials targeting weight loss have shown a reduction in cholesterol and triglycerides, at least in the medium term (37). The most beneficial diet for improving lipids remains debated and dissecting which of the alterations in lipids are due to weight loss or due to the specific composition of the diet is difficult.

The literature regarding the use of dietary modification for the treatment of familial hyperlipidemic syndromes in pregnancy discusses the use of very low-fat diets (<20%). These diets are used in severe hypertriglyceridemia to assist in reducing the markedly elevated levels of chylomicrons (34), which are poorly cleared in the setting of very elevated levels of fasting triglycerides. Such an extremely low-fat diet has been used in pregnancy in women with familial hyperlipidemic syndromes (34) but has not been investigated for broader use. One concern regarding the potential use of very low-fat diets in women without hyperlipidemic syndromes is whether there would be any adverse effect on fetal brain development. A previous observational study has reported the association of very low (<10th centile) maternal total cholesterol with increased rates of microcephaly (25).

One large study specifically targeted the lowering of maternal cholesterol in uncomplicated pregnancy, the Cardiovascular Risk Reduction Diet in Pregnancy (CARRDIP) trial. This open-label, randomized trial used a cholesterol-lowering diet from 19 weeks in 290 healthy pregnant women with BMI 19–32 kg/m^2. Maternal total and LDL-C were lower in the intervention group, as were HDL-C levels, with no effect on maternal triglycerides seen. There was a lower rate of delivery before 37 weeks (0.7 vs. 7.4% of control women) (38). There was no difference in rates of hypertensive disorders or in birth weight. Infant head circumference was reported as not different between treatment groups. The CARRDIP study finding of a reduction in preterm delivery in women on a low-cholesterol diet holds promise but needs replication and further examination of longer-term infant neurological development.

Other studies examining dietary modifications have not been aimed specifically at altering maternal lipids but rather at managing weight or glycemic control. The use of a hypocaloric diet (without changing proportions of carbohydrate/fat/protein) in comparison with subcutaneous insulin therapy over 1 week in obese women with GDM reduced maternal triglycerides (39). The short-term (4 days) use of a low-carbohydrate diet in women with GDM resulted in increased free fatty acids and a trend to increased maternal fasting triglycerides with no change in insulin response to a 50-g load while on each diet (40). Overweight and obese pregnant women randomized to either a low glycemic load or low-fat diet from 19 weeks gestation onward showed a greater increase in maternal total cholesterol and smaller increase in maternal triglycerides in those on a low-glycemic-load diet from early to late pregnancy (41). There was no difference in gestation-adjusted infant birth weight or infant anthropometry but a greater infant head circumference in infants in the low-glycemic-load group (41). Dietary modification aimed at weight reduction can alter maternal lipids, and the low-glycemic-index, low-carbohydrate diet frequently used in the management of diabetes in pregnancy may have differential effects on maternal cholesterol, free fatty acids, and triglycerides.

Exercise is also commonly used for control of maternal glycemia and weight gain, but few exercise studies have examined the change in maternal lipids. The most consistent reported change in maternal lipids in the acute response to exercise is an increase in triglycerides and free fatty acids compared with the resting state. A longer-term randomized trial of aerobic exercise in the second half of pregnancy in 84 healthy women showed a trend toward lower maternal free fatty acid levels with no change in maternal weight compared with control subjects (42). A trial of postprandial walking (for 20 min after each meal) in women with type 1 diabetes showed a reduction in fasting maternal triglycerides (43). Longer-term exercise studies in pregnancy show a reduction in maternal free fatty acids and triglycerides, but larger studies are needed to examine the potential fetal or maternal effects of this reduction.

The short-term and long-term impacts of dietary and exercise interventions differ. They are able to influence maternal lipids, but the overall impact of the altered lipid levels on maternal and infant health, weight, and body composition requires further study.

Metformin

Metformin crosses the placenta (44) and thereby has the potential to alter glucose and lipid metabolism in the mother, placenta, and infant. Maternal and cord blood lipids have recently been examined in the Metformin in Gestational diabetes (MiG) trial (45). This multicenter, randomized trial recruited 363 women to metformin treatment and 388 to insulin at initiation of pharmacological treatment for their GDM. A proportion (46.3%) of women randomized to metformin required supplemental insulin to meet the required glycemic targets. In the examination of lipids, maternal plasma triglycerides increased more from randomization (~30 weeks) to 36 weeks gestation in women treated with metformin than in those treated with insulin. This difference may be due to insulin suppressing the normal rise in maternal triglycerides in late gestation to a greater extent than metformin. The difference found between these two groups in the MiG trial was of unclear clinical significance since there were no other differences in maternal and cord plasma lipids or neonatal anthropometry. However, maternal triglycerides and measures of glucose control at 36 weeks were associated with birth weight >90th centile. Examination of whether there is altered placental lipid

processing and further examination of fetal lipid metabolism in the setting of metformin use would be important in a decision to deliberately use metformin to target lipid abnormalities in pregnancy.

Insulin

Insulin therapy alters lipids. It decreases lipolysis in adipose tissue, thereby reducing free fatty acids and hepatic synthesis of triglycerides. Insulin therapy reduces triglycerides by 10 to ~40% in both type 1 and type 2 diabetes (46). The altered composition of lipoproteins found in diabetes is improved but not completely resolved by achieving good glycemic control thorough intensive insulin therapy (46).

Insulin therapy has the potential to influence maternal lipids in different ways than oral hypoglycemic therapies in pregnancy. In the MiG trial, as described above, women allocated to insulin had a lower increase in triglycerides from the second to the third trimester but there were no clear effects of this on infant or pregnancy outcome. There is no evidence concerning the use of insulin to deliberately manipulate maternal lipids in the setting of diabetes in pregnancy.

Omega-3 Fatty Acids (n-3 Fatty Acids, Fish Oil, and LC-PUFA)

Omega-3 fatty acids have been trialed in pregnancy for prevention of preterm birth, improvement of infant visual and cognitive development, allergy prevention in the infant, and maternal mental health. Omega-3 fatty acids reduce maternal triglyceride levels by decreasing hepatic production of triglyceride-containing lipoproteins and by enhancing clearance of triglycerides from circulating lipoproteins (47). They are commonly used as monotherapy or in conjunction with fibrates and niacin (nicotinic acid) to lower triglyceride levels in the nonpregnant population. Administration of omega-3 fatty acids is associated with a 20–50% decrease in triglyceride levels, with a possible increase or no change in LDL-C and HDL-C (47). Of relevance to the current review are studies examining the impact on maternal lipids, and on fetal growth or pregnancy complications, such as gestational hypertension and preeclampsia.

Omega-3 fatty acid supplementation has been examined for prevention of GDM. A systematic review of omega-3 supplementation in pregnancy found no difference in the rates of GDM (48). The DHA to Optimize Mother Infant Outcome (DOMInO) trial (49) was a multicenter Australian study including 2,399 women allocated to either 800 mg/day of docosahexaenoic acid and 100 mg eicosapentaenoic acid or vegetable oil capsules. Women were enrolled at a mean of 19 weeks gestation, with a mean BMI of 26 kg/m^2, primarily Caucasian, and ~68% had completed more than secondary education and 39% were primiparous. The primary outcomes of the main trial were risk of depressed maternal mood and cognitive development in the offspring. A post hoc examination of this trial found no difference in the risk of developing GDM or preeclampsia. However, these were largely healthy pregnant women who were at low risk for either of these complications.

Studies have also examined the possible effects of omega-3 fatty acids on infant growth. Systematic reviews (50) and meta-analyses (48) of infant growth and birth weight in humans have reported a greater head circumference, infant length, and birth weight in infants whose mothers were administered omega-3 fatty acids. However, one possible confounding factor in this is that the use of omega-3 supplements seems to slightly prolong the duration of pregnancy (albeit with a weighted mean difference of 1.57 days [48]). A systematic review examining the effect of maternal supplementation during gestation on infant body composition found only two trials that administered omega-3 fatty acids during pregnancy. These had quite different designs and reported disparate results, with one showing a reduction in infant BMI *z* score at 21 months age and the other showing no effect at 7 years of age (50). In the short term, omega-3 fatty acid supplementation seems to increase infant growth but the longer-term effect is unclear.

Omega-3 fatty acids are a possible pharmacological therapy for use in pregnancies complicated by diabetes. They have been shown to lower triglycerides in the nonpregnant state and are generally safe for use in pregnancy. Their influence on infant size and body composition requires clarification. Additionally, omega-3 fatty acids for manipulation of maternal lipids and examination of influence on pregnancy complications and fetal growth have not as yet been subjected to a randomized control trial in women with diabetes. Undertaking this will be complicated by the presence of fish oil in common pregnancy supplements.

Statins (αHMG-CoA-Reductase Inhibitors)

Statin use in pregnancy has been discouraged due to concerns over their pleomorphic effects on metabolism and potential teratogenicity, although there are few large studies examining this risk. Statins primarily reduce the synthesis of cholesterol. They also have anti-inflammatory, antithrombotic, and antioxidant effects. In addition to reducing triglycerides by 10–20%, statin therapy decreases LDL-C, non–HDL-C, and markers of inflammation. A recent systematic review and meta-analysis examining the use of statins in pregnancy in both human and animals suggested that statins are unlikely to be teratogenic, with no recurrent pattern of malformations reported in animal studies (51). In studies where increased rates of congenital malformation were reported, the doses used were much higher than those used in humans (51). However, statins have been shown to have effects on placental development in vitro, with decreased migration of cytotrophoblasts and syncytiotrophoblasts (52), and the effects of statin therapy on human pregnancy outcomes are based on small numbers of gestations. More data will soon be available, with two randomized controlled trials examining the use of pravastatin in women at high risk of early-onset preeclampsia currently under way (53,54). Statins are a possible therapy for the latter part of pregnancy at least, but further studies are warranted before using statins widely in pregnancy.

Niacin (Vitamin B3, Nicotinic Acid)

Niacin use in pregnancy has been reported in case reports only, and pharmacological doses are considerably higher than the recommended daily intake (34). Niacin has multiple effects on lipids, decreasing triglycerides and LDL-C while raising HDL-C (55). The reduction in triglycerides and LDL-C occurs through decreasing adipose tissue lipolysis and free fatty acid release. Hepatic synthesis of VLDL and triglycerides is

also reduced (55). Niacin cannot be recommended for widespread use at this point.

Fibrates

There are case reports of the use of fenofibrate at various stages of pregnancy without teratogenic effects (34). Fibrates activate peroxisome proliferator–activated receptor α (PPARα), regulating the transcription of multiple proteins involved in lipid metabolism and thereby reducing triglyceride concentration, increasing LDL-C clearance, and increasing HDL-C levels. Given the sparse accounts of use, fibrates cannot be recommended for widespread use in pregnancy at the current time.

Resveratrol

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) has been reported to have multiple metabolic effects, including increased insulin sensitivity, and influences cholesterol metabolism and atherosclerosis as well as being anti-inflammatory and antitumorigenic (56). Lipid effects reported in human trials include decreased LDL-C, apoB, and triglycerides and lower intrahepatic lipid content, but these effects are not reliably reported, with other studies showing no such modifications (56). Resveratrol administered to the dam has been detected in fetal plasma in rodents, but no data exists in humans. A recent review examined the possibility of using resveratrol for complications of diabetic pregnancy and reports a reduction in maternal glucose, cholesterol, and triglycerides, as well as a reduction in neural tube defects, in rodent models of diabetic pregnancy (57). Human pregnancy studies have not yet been undertaken.

FURTHER RESEARCH

The current evidence suggests a potential role for abnormal maternal lipid metabolism in promoting excess fetal growth and adiposity but does not prove causality. Prior to embarking on the routine use of any of these treatments, a number of further investigations need to be undertaken to fill major evidence gaps:

- The epidemiology and associations of maternal lipids with fetal outcomes needs expansion, particularly in type 2 diabetes where data are currently based on very small numbers.
- Systematic exploration of the impact of coexistent maternal factors such as obesity with diabetes on maternal lipids.
- Closer examination of maternal lipids, placental lipid handling, and infant adiposity in women with familial lipid syndromes may well shed light on underlying mechanisms and whether lipids are truly associated with adverse pregnancy outcomes.
- Almost all lipid studies have been undertaken on fasting blood samples: examination of whether postprandial maternal hypertriglyceridemia and chylomicronemia have an association with fetal growth as has been found with postprandial glucose.
- Consideration of gestational age at the time of measurement of lipids needs further exploration. Early pregnancy measurement may give a better prognostic indication for later pregnancy complications.
- Further animal studies, particularly in primate models, assessing the fetal effects of the pharmacological options.
- Many of the therapies mentioned above have potential to alter not only maternal metabolism but placental metabolism and this should be investigated in greater detail.
- Carefully designed interventional studies aimed at modifying maternal lipid levels in high-risk women. The most obvious pharmacological method to use initially would be omega-3 fatty acid supplements as these have been found to be relatively safe in pregnancy. The targets for maternal lipids in such trials would need to be based on large epidemiological studies examining maternal lipids and pregnancy outcomes in a continuous manner.

As in all pregnancy-related trials, safety of potential treatments, both for mother and baby, would be of paramount importance.

CONCLUSIONS

There is evidence that abnormal maternal lipids in pregnancy are associated with adverse pregnancy outcomes for mother and infant and that maternal lipids are abnormal in the setting of diabetes. Given the challenges in managing maternal glycemia in current clinical practice, the option of adding another method of correcting maternal metabolism in the diabetic pregnancy is alluring, but considerable work needs to be done before we can routinely adjust maternal lipids in pregnancy.

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