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Review

The current status of lipoprotein (a) in pregnancy: A literature review

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ABSTRACT

Background and purpose: Lipoprotein (Lp) (a) is a neglected element of the blood lipid profile. It is now recognized as a determinant of coronary heart disease progression and its role in atherosclerosis and its ability to induce thrombosis make it potentially important in the course of normal and complicated pregnancies. Pregnancy involves a major transformation of metabolism to sustain fetal growth. Multiple studies have been conducted on Lp(a) in pregnancy, and it is timely to synthesize and evaluate this evidence.

Methods and subjects: We reviewed the MEDLINE database for all articles published concerning "lipoprotein a" and "pregnancy" from May 2003 to May 2012. A previous comprehensive review assessed the literature up to May 2003.

Results: We critically analyzed 14 studies detailing the effect of complications in pregnancy on Lp(a) profile, and subsequent pregnancy outcomes where available. Studies evaluating the normal metabolic response to pregnancy, pregnancies complicated by pre-eclampsia and intra-uterine growth restriction were reviewed.

Conclusions: A substantial mass of data has accumulated describing Lp(a) changes in pregnancy. The diversity of study design limits the ability to draw broad-ranging conclusions, but brings into focus the important questions remaining, which we discuss.

Contents

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Introduction

Lipoprotein (Lp) (a) is a subclass of lipoprotein, consisting of a low-density lipoprotein (LDL) covalently bound via its apolipoprotein B100 portion to apolipoprotein (apo) (a) [1]. It was discovered by Berg in 1963 and increased levels of Lp(a) have been correlated with increased risk of coronary heart disease (CHD), although the nature of this relationship is not clear [2,3]. Lp(a) forms an important part of the clinical biomarker profile of patients with CHD and heart failure [4,5]. In addition to the role of Lp(a) in atherosclerosis, the apo(a) element of Lp(a) has a structure similar to plasminogen, allowing Lp(a) particles to reduce the physiological fibrinolytic activity of plasminogen by competitively binding endothelial plasminogen receptors [6]. It is this pro-thrombotic effect, together with Lp(a) accumulation in atherosclerotic lesions, that is thought to predispose those with high levels to CHD [7].

The plasma concentration of Lp(a) is mainly governed by the gene locus for apo(a), located on chromosome 6. Although high levels of Lp(a) are inherited in a dominant fashion, other genes and other factors (diet, hormones and disease states) can influence Lp(a) concentrations [8,9]. Polymorphisms in the apo(a) gene produce isoforms of apo(a) of different sizes. The smaller the isoform, the higher the Lp(a) concentration – a phenomenon which accounts for 40% of the variation of Lp(a) concentration [10,11]. The relationship between apo(a) isoform size and CHD and vascular disease is complex. A large systematic review from 2010 showed a twofold higher risk of CHD and ischemic stroke in subjects with smaller apo(a) isoforms [12]. Other studies have suggested smaller apo(a) isoforms predict angina symptoms better than Lp(a) concentrations [13]. However, more recent studies have found that the apo(a) isoform size contributes little to the relationship between Lp(a) and CHD and is not an independent risk factor for CHD [14]. Therefore, there is evidence that both Lp(a) isoform size and concentration and the interaction of these variables with patient-specific factors are important in determining CHD and stroke risk. The precise nature of this interaction needs further elucidation.

The production of Lp(a) occurs at the hepatocyte surface and clearance is via the kidney [15]. The standard reference plasma concentration of Lp(a) is <0.1 to >300 mg/dL in Caucasians, with mean concentrations of 15 mg/dL [16]. Although plasma levels of Lp(a) are similar in both men and women, gender influences the cardiovascular risk. At similarly high levels of plasma Lp(a), women are more likely to experience CHD than men [2,17].

What is known about Lp(a) in pregnancy?

Lp(a) has been studied in both normal pregnancies and pregnancies complicated by various disease states, e.g. pre-eclampsia. In healthy pregnant women, lipid metabolism is altered over the course of pregnancy to result in a hyperlipidemic third-trimester state [18–20]. This is due to a combination of the direct effect of estrogen on lipid synthesis in the liver, as well as a state of relative insulin resistance (thereby releasing free fatty acids from adipocytes). Triglyceride levels increase markedly, with cholesterol and phospholipid levels increasing more modestly [21]. Hyperlipidemia in pregnancy provides a functional reservoir for the fetus – allowing cholesterol, for example, to be used for building fetal cellular membranes, steroid hormones, and bile acids [22,23]. Pre-eclampsia is a disorder of uncertain pathogenesis, characterized by hypertension and proteinuria from the 20th week of pregnancy onwards. Endothelial cell injury, resulting in coagulation and vasoconstriction, is thought to play a role in its pathogenesis [24]. The similarity between this and the process of atherosclerosis – together with the antifibrinolytic properties of Lp(a) – has led researchers to consider the role of Lp(a) in pre-eclampsia. A prothombotic state has also been postulated to be important in the pathogenesis of other diseases of pregnancy including intrauterine growth restriction (IUGR) (defined as a fetus that is pathologically small, often a product of pre-eclampsia) and recurrent pregnancy loss (RPL) (defined as 3 or more consecutive pregnancies miscarried at <20 weeks gestation) [25].

A number of unanswered questions remain. What is the role of Lp(a) in both normal and complicated pregnancies? Does Lp(a) have a role in pregnancies complicated by conditions other than pre-eclampsia and IUGR? If Lp(a) is increased in normal pregnancy, what is the physiological significance of this? If not, what are its exact effects? What is the mechanism of the increased Lp(a) concentration – is it attributable more to genetics or to environment (e.g. change in diet)? What impact does a raised Lp(a) in pregnancy have on the developing fetus (and its future cardiovascular risk)? How does having a twin pregnancy impact upon levels of Lp(a)? Answers to these questions will determine how Lp(a) levels should be managed in pregnancy.

Methods

Search criteria

The literature pertaining to Lp(a) in pregnancy was comprehensively reviewed from January 1966 up to May 2003 by Manten et al. in 2005 [26]. The authors concluded that studies up to 2003 yielded diverse results, with no consensus on the role of Lp(a) in any condition studied (normal pregnancy, pregnancies complicated by pre-eclampsia or IUGR) – in part due to differing methodologies. This will be addressed further in "Discussion" section.

In this review, a MEDLINE search was performed to identify relevant articles published between May 2003 and May 2012, written in the English language. Search items were: "Lipoprotein a in pregnancy", "Lipoprotein a in normal pregnancy", "Lipoprotein a in complicated pregnancy", "Lipoprotein a in pre-eclampsia/preeclampsia" and "Lipoprotein a in IUGR". All relevant articles were included in the analysis. Other relevant papers were identified through the reference sections of articles. Articles were excluded if they pertained to neonatal sequelae of high Lp(a).

Results

Study characteristics

A total of 14 relevant articles were identified (Tables 1 and 2). Eight of these were case–control studies, one was interventional, one was longitudinal, three were cross-sectional and, one was both case–control and longitudinal. The number of subjects ranged from 19 to 544. Most studies had subjects either of only Caucasian or unknown ethnicity. Most authors used a method of measuring Lp(a) that was not apo(a) isoform-independent, which – given that Lp(a) concentration is influenced by apo(a) isoform size – can lead to over- or under-estimations of Lp(a) concentration. Most did not analyze the nature of the apo(a) isoforms. Most of the studies used women in their 3rd trimester of pregnancy as subjects.

Nine of the studies focused on comparing Lp(a) levels in healthy pregnant women to Lp(a) levels in women with pre-eclampsia in the 3rd trimester of pregnancy (Table 1) [27–35]. One of these nine studies also looked at Lp(a) levels in the fetus [30] and one of these studies additionally compared Lp(a) levels in women with a history of IUGR [31]. Two of the studies examined Lp(a) levels in healthy pregnant women [36,37], one of which compared levels in healthy non-pregnant women [36]. One study examined Lp(a) levels in pregnant women with familial hypercholesterolemia (FH) compared to healthy pregnant controls [38]. And two of the studies examined Lp(a) levels in women with a history of RPL [39,40].

Table 1
Studies investigating the role of Lp(a) in pregnancies affected by pre-eclampsia.

Study	Design	No. pts	Population characteristics	Age of women (years)	Ethnicity	Apo(a) isoform typing	Method of Lp(a) measurement	Results	Pregnancy outcomes
Bukan et al. [28]	CC	41	16 women with normal pregnancies, 25 women with pre-eclampsia (2nd/3rd trimesters)	Subjects 33.64 ± 6.05, controls 35.2 ± 4.8	U	No	Nephelometry	No difference in Lp(a) levels between subjects with pre-eclampsia vs healthy controls	N/A
Demir et al. [27]	CC	70	35 women with normal pregnancies, 35 women with pre-eclampsia (all 3rd trimester)	Subjects 28.8 ± 6.6, controls 29.4 ± 4.1	U	No	Nephelometry	Increased levels of Lp(a) in subjects with pre-eclampsia vs healthy controls ($p < 0.0001$)	Not assessed
Parvin et al. [29]	CC	60	30 women with normal pregnancies, 30 women with pre-eclampsia (all 3rd trimester)	Subjects 23.73 ± 4.33, controls 23.40 ± 3.04	U	No	Nephelometry	Increased levels of Lp(a) in subjects with pre-eclampsia vs healthy controls ($p < 0.001$)	Not assessed
Catarino et al. [30]	CC	88	42 women with normal pregnancies, 46 women with pre-eclampsia (all 3rd trimester) (maternal blood samples and fetal umbilical cord blood samples)	Subjects 29.7 ± 5.3, controls 30.4 ± 5.7 [GA of subjects = 37.0 (34–38), GA of control = 38.5 (38–39.3)]	U	No	Immunoturbidimetry	No difference in Lp(a) levels between subjects with pre-eclampsia vs healthy controls (both maternal and fetal samples)	N/A
Manten et al. [31]	CC	368	53 women with a history of normal pregnancy, 256 women with a history of pre-eclampsia, 59 women with a history of IUGR (all studied at least 3 months PP)	Subjects with a history of pre-eclampsia 31 ± 4 (statistically significant difference from controls), subjects with a history of IUGR 32 ± 4, controls 33 ± 4	C	No	Apo(a) isoform-independent ELISA	No difference in Lp(a) levels between subjects with pre-eclampsia vs IUGR vs healthy controls	N/A
Wang et al. [33]	I	26	13 women with normal pregnancies, 13 women with pre-eclampsia (outcome of study to assess effect of heparin-mediated apheresis) (women with pre-eclampsia in both 2nd/3rd trimesters, women with normal pregnancies in 3rd trimester)	Subjects 33.0 (23.9–39.8), controls 33.9 (24.8–38.4)	C	No	Immunoturbidimetry	No difference in Lp(a) levels between subjects with pre-eclampsia vs healthy controls Heparin-mediated apheresis resulted in a reduction in Lp(a) levels (by 49%) ($p < 0.001$)	Of the 9 neonates born to mothers with pre-eclampsia treated with heparin-mediated apheresis, 8 had good clinical outcomes. 1 died of late-onset sepsis
Bayhan et al. [34]	CS	73	20 women with normal pregnancies, 25 women with mild pre-eclampsia, 28 women with severe pre-eclampsia (all in 3rd trimester)	–	–	–	Nephelometry	Increased levels of Lp(a) in subjects with mild and severe pre-eclampsia vs healthy controls Positive correlation between levels of Lp(a) and BMI in severely pre-eclamptic women ($p = 0.008$)	–
Baksu et al. [35]	CS	131	40 healthy women with normal pregnancies, 48 women with mild pre-eclampsia, 43 women with severe pre-eclampsia (all in 3rd trimester)	Subjects with severe pre-eclampsia 26.7 (17.0–38.0), subjects with mild pre-eclampsia 28.3 (19.0–43.0), controls 26.7 (19.0–37.0)	U	No	Turbidimetry	No difference in levels of Lp(a) between subjects with pre-eclampsia vs healthy controls	N/A

Table 1 (*Continued*)

Study	Design	No. pts	Population characteristics	Age of women (years)	Ethnicity	Apo(a) isoform typing	Method of Lp(a) measurement	Results	Pregnancy outcomes
Manten et al. [32]	CS	70	20 healthy non-pregnant controls, 50 pregnant women (20 healthy pregnant controls, 20 with mild pre-eclampsia and 10 with severe pre-eclampsia) (severe pre-eclamptics in 2nd/3rd trimester, all others in 3rd trimester)	Subjects with severe pre-eclampsia 32 (19–37), subjects with mild pre-eclampsia 29 (22–37), controls with healthy pregnancies 29 (24–37), non-pregnant controls 27 (24–37)	C	Yes	Apo(a) isoform-independent ELISA	Decreased levels of Lp(a) in subjects with severe pre-eclampsia vs mild pre-eclampsia ($p < 0.05$) (note possibility of bias from significant difference in GA at sampling) No difference in levels of Lp(a) between subjects with mild pre-eclampsia vs healthy pregnant controls vs non-pregnant controls No difference in distribution of apo(a) isoforms between subjects vs controls	Reduced birthweight of infants born to severely pre-eclamptic mothers (compared to infants born to mildly pre-eclamptic mothers, who in turn had reduced birthweight compared to infants born to healthy mothers)

Lp(a), lipoprotein (a); CC, case–control; CS, cross-sectional; L, longitudinal; I, interventional; PP, post-partum; GA, gestational age; –, information not available; C, Caucasian; U, unknown; N/A, non-applicable (where no difference in Lp(a) levels were recorded between subject and control groups).

The results from these studies are shown in Table 1 (studies pertaining to pre-eclampsia) and Table 2 (studies pertaining to normal pregnancy or other pregnancy conditions).

What is the role of Lp(a) in normal pregnancy?

Two studies focused exclusively on normal pregnancies. Both showed increased levels of Lp(a) compared to non-pregnant controls. The case–control study of Lippi et al. showed increased levels of Lp(a) in women in their 2nd/3rd trimester compared to women in their 1st trimester/non-pregnant women [36]. The longitudinal study of Manten et al. showed that levels of Lp(a) increased up to the 35th week of gestation, then declined slightly before delivery, before falling below 1st trimester levels by 3–5 months post-delivery [37]. The longitudinal study design allowed the authors to develop a formula for calculating reference Lp(a) levels according to gestational age (GA). Two mechanisms were proposed by the authors to account for the rise in Lp(a). First, that the physiological hyperlipidemia of pregnancy induces endothelial cell dysfunction and that Lp(a) – acting in its role as an acute-phase protein – binds to endothelial cells and promotes delivery of cholesterol to aid cellular regeneration. Second, that increased levels of Lp(a) may act to fulfill the demand for increased steroid hormone synthesis in pregnancy. The decrease in Lp(a) toward delivery may be accounted for by increased consumption secondary to increased endothelial cell damage.

What is the role of Lp(a) in pregnancy complicated by pre-eclampsia?

Nine studies evaluated Lp(a) in pre-eclampsia [one of which additionally compared Lp(a) levels in women with a history of IUGR]. Three showed an increased level of Lp(a) in subjects with pre-eclampsia compared to healthy pregnant controls [27,29,34]. Two of these were case–control studies and one was cross-sectional. No putative mechanisms for this increase in Lp(a) were postulated.

One of the studies (cross-sectional design) showed a decreased level of Lp(a) in subjects with severe pre-eclampsia [32]. Manten et al. [32] postulated that this was due to more extensive endothelial damage in severe pre-eclampsia (as compared to mild, or no pre-eclampsia) and hence higher consumption of Lp(a) as an acute-phase protein. The authors also acknowledge that the significant difference in GA of their subjects at sampling (208 days for patients with severe pre-eclampsia, compared to 273 days for patients with mild pre-eclampsia) could have affected outcomes.

The rest of the nine studies (three case–control, one cross-sectional, one interventional) showed that there was no difference in Lp(a) levels in subjects with pre-eclampsia compared to healthy controls [28,30,31,33,35]. An explanation postulated by Manten et al., who examined women with a history of pre-eclampsia (rather than experiencing pre-eclampsia at the time of blood sampling), is that the rise in Lp(a) may be transient during pregnancy [31].

What is the role of Lp(a) in pregnancy complicated by IUGR?

Only one study explored the role of Lp(a) in IUGR [31]. This case–control study showed that there was no difference between levels of Lp(a) in women with a history of IUGR compared to women with a history of normal pregnancy. The authors postulated that this may be due to a transient rise in Lp(a) during pregnancy, with return to normal levels post-delivery.

Table 2
Studies investigating the role of Lp(a) in normal pregnancies and pregnancies affected by conditions other than pre-eclampsia.

Study	Design	No. pts	Population characteristics	Age of women (years)	Ethnicity	Apo(a) isoform typing	Method of Lp(a) measurement	Results	Pregnancy outcomes
Lippi et al. [36]	CC	78	57 women with normal pregnancies (20 in the 1st trimester, 20 in the 2nd trimester, 17 in the 3rd trimester), 21 non-pregnant women	–	–	–	Nephelometry	Increased Lp(a) levels in subjects in 2nd/3rd trimesters vs 1st trimester/non-pregnant controls	–
Amundsen et al. [38]	CC/L	171	149 healthy women with normal pregnancies, 22 pregnant women with FH (evaluated at 17–20 weeks, 24, 30, 36 weeks and 3–6 months PP) (21/22 of women with FH had statin-therapy prior to pregnancy)	Subjects 31.4 ± 4.2, controls 29.8 ± 3.4	U	No	Immunoturbidimetry	No change in Lp(a) levels in FH women during course of pregnancy No comparison between Lp(a) levels in FH and healthy controls	No difference in pregnancy outcome between FH and control groups
Glueck et al. [40]	CC	544	92 women with a history of 1 or more pregnancies and 1 miscarriage, 72 women with a history of RPL, 380 women with a history of 1 or more pregnancies and 0 miscarriages	U	93% C	No	U	No difference in levels of Lp(a) between subjects with history of miscarriage vs RPL vs healthy controls	N/A
Krause et al. [39]	CC	266	133 age-matched healthy controls, 133 women with unexplained RPL	Subjects 29 (17–40), controls 28.5 (18–40) (age at first miscarriage)	C	Yes (sub-group analysis)	Apo(a) isoform-independent ELISA	Increased levels of Lp(a) in subjects with unexplained recurrent miscarriage vs healthy controls ($p < 0.000$) Increased levels of small apo(a) isoforms in subjects with unexplained recurrent miscarriage vs healthy controls ($p = 0.002$)	Pregnancy outcome different between groups based on study definition/inclusion criteria (RPL vs controls)
Manten et al. [37]	L	19	19 healthy women with normal pregnancies (assessed every 4 weeks from 9 to 14 weeks GA, during labor and at 2–4 weeks and 3–5 months after delivery)	30.5 ± 4.4	C	Yes	Apo(a) isoform-independent ELISA	Levels of Lp(a) increased until 35 weeks of pregnancy, decreased slightly until delivery and then fell to values below first-trimester levels No difference in distribution of apo(a) isoforms between subjects vs other control populations	Mean GA = 278 days Mean birth-weight = 3435 g [Longitudinal study, therefore no comparison group]

Lp(a), lipoprotein (a); CC, case–control; CS, cross-sectional; L, longitudinal; FH, familial hypercholesterolemia; PP, post-partum; RPL, recurrent pregnancy loss; Apo(a), apolipoprotein (a); ELISA, enzyme-linked immunoassay; GA, gestational age; –, information not available; C, Caucasian; U, unknown; N/A, non-applicable (where no difference in Lp(a) levels were recorded between subject and control groups).

What is the role of Lp(a) in pregnancy complicated by RPL?

Two studies evaluated levels of Lp(a) in women with a history of RPL. Both were of case–control design. One (Glueck et al.) showed no difference in Lp(a) levels in women with a history of one miscarriage, compared to those with RPL or healthy controls [40]. The other study (Krause et al.) showed increased levels of Lp(a) in women with a history of RPL [39]. The authors postulated that this could be due to the association of Lp(a) with a hypofibrinolytic state – promoting thrombosis and hence miscarriage.

What is the role of Lp(a) in pregnancy complicated by other conditions?

One study investigated levels of Lp(a) in pregnant women with FH (Amundsen et al.) [38]. All the women (except one) with FH in this study had been treated with both dietary modification and statins prior to pregnancy. Upon planning of pregnancy, statins were stopped in all women (except one, who continued to take statins into the first month of pregnancy). The study design was both longitudinal and case–control and showed no change in Lp(a) levels in pregnant women with FH during the course of pregnancy. No specific comparison was made between Lp(a) levels in pregnant women with FH, compared to healthy pregnant controls.

Discussion

The role of Lp(a) in normal pregnancy

The two studies exclusively pertaining to Lp(a) levels in normal pregnancy found that Lp(a) levels were raised in normal pregnancy compared to non-pregnant controls and that Lp(a) levels increased during the course of pregnancy, respectively [36,37]. This has been shown by previous studies, albeit peak Lp(a) concentrations being noted at different gestational ages [41–43]. The mechanism for this rise has variously been postulated to be due to Lp(a) acting as an acute phase protein in response to endothelial cell damage, or due to metabolic demand for substrates for increased hormone synthesis [37,43]. Other theories include Lp(a) – in its role as a hypofibrinolytic agent – being necessary for normal placental development [41]. Previous studies in normal pregnancy have found different results, however, with several demonstrating no change in Lp(a) during the course of pregnancy [44,45]. One study, performed with both longitudinal and cross-sectional designs, had contrasting findings. When changes in Lp(a) were evaluated in pregnancy by longitudinal follow-up, Lp(a) concentrations increased during pregnancy. However, when Lp(a) concentrations were evaluated in pregnancy by cross-sectional design, there were no significant changes in median Lp(a) levels among groups of pregnant women of different gestational ages (1st vs 2nd vs 3rd trimesters) [46].

The role of Lp(a) in pre-eclampsia

The studies evaluating Lp(a) in pre-eclamptic patients showed variously an increased, decreased, or equivalent level of Lp(a) in pre-eclamptic patients compared to healthy pregnant controls [27–35]. These non-uniform findings have been similarly produced in previous papers. Some studies suggest that pre-eclampsia is associated with increased Lp(a) [47–51], while others suggest that there is no significant difference in the levels of Lp(a) between pre-eclampsia and healthy pregnancy [46,52,53]. Increased levels of Lp(a) in pre-eclampsia are thought to be due to more widespread endothelial cell damage, necessitating increased levels of Lp(a) to act as both an acute phase protein and as a vehicle for cholesterol deposition at the site of dysfunction (the endothelial cell damage being caused by likely abnormal placental implantation). Where no change in the level of Lp(a) has been noted in pre-eclampsia, this has been postulated to be due to endothelial cell damage only being a local (uterine) change in pre-eclampsia, rather than a systemic one [52].

The role of Lp(a) in other conditions affecting pregnancy

The limited number of studies investigating Lp(a) levels in the context of IUGR, RPL, and FH have few other papers to support or refute their findings. The study exploring Lp(a) levels in IUGR found no difference in levels between women with a history of IUGR and healthy controls [31]. In previous studies, however, increased levels of Lp(a) have been noted in association with IUGR [48,49]. The mechanism for this has been suggested to be due to the hypofibrinolytic (and hence pro-thrombotic) action of Lp(a), resulting in poor fetal growth. The findings that RPL may be linked with higher Lp(a) levels have been shown previously and have been postulated to occur through a similar mechanism [49].

The impact of Lp(a) on pregnancy outcomes

In six of the 14 studies, assessing the impact of Lp(a) on pregnancy outcome was not applicable – as the authors found no difference in Lp(a) levels between subjects and controls [28,30,31,33,35]. In two of the 14 studies, insufficient information was available [34,36]. In two of the 14 studies, pregnancy outcomes were potentially assessable but were not formally assessed [27,29]. In the study by Wang et al., it was shown that there was no difference in Lp(a) levels between subjects and controls [33]. However, the principle outcome of the study was to evaluate the effects of heparin-mediated apheresis – and pregnancy outcomes in this study (8 healthy neonates, 1 death from late-onset sepsis) must be viewed in this context. In the study by Manten et al., it was shown that reduced birthweight was associated with severe pre-eclampsia, which was in turn associated with reduced levels of Lp(a) [32]. In the study by Krause et al., pregnancy outcome was an intrinsic aspect of recruitment to the study (RPL vs healthy controls) and the authors found higher levels of Lp(a) in subjects with RPL [39]. In the study by Manten et al., pregnancy outcomes were recorded, but the impact of Lp(a) could not be assessed as the study was longitudinal, rather than case–control, in design [37]. In summary, therefore, the articles evaluated in this review do not answer the question as to the impact of Lp(a) on pregnancy outcome. This is in part due to a failure to measure outcomes and in part due to no difference in Lp(a) levels being recorded between subjects and healthy controls. In those studies where differences in Lp(a) levels were noted, a greater range of pregnancy outcomes would have been useful to evaluate. The question, therefore, remains as to whether, if Lp(a) is definitively shown to be raised in pre-eclampsia, whether it is a cause of pre-eclampsia, a consequence, or a simple bystander.

Unanswered questions

Nearly all of the studies published since May 2003 have focused on the concentration of Lp(a) in normal pregnancy and pregnancies affected by pre-eclampsia. Few articles attempted to evaluate a mechanism for raised Lp(a), or – beyond theorizing – investigate the reasons for raised Lp(a). A few of the questions posed have been raised by some studies – including evaluating potential therapeutic options and evaluating the effects of Lp(a) on the fetus. Wang et al. pointed to a role for heparin-mediated apheresis to enable reduction of raised Lp(a) in the context of pre-eclampsia [33]. Catarino et al. showed that there was no difference in Lp(a) levels in fetuses affected by pre-eclampsia (compared to healthy

controls) [30]. Other recent studies – beyond the search parameters of this review – have begun to explore the impact of high maternal Lp(a) and/or high fetal Lp(a) on neonatal outcomes [54,55]. It is important to note that combining this analysis with that of pre-2003 studies would not alter our conclusions.

Limitations of articles reviewed

The fact that only 14 articles were identified as directly pertaining to the role of Lp(a) in pregnancy since May 2003 shows that, despite controversy, little evidence is available to resolve these issues. As a result, it is difficult to draw conclusions from the limited data available. Although 11 out of 14 of the studies had a sample size of over 50 (and of the three that did not, two were interventional or longitudinal), most of the studies were either case–control or cross-sectional in design, which renders conclusions on causality or mechanisms difficult to attain.

In addition, a number of the key recommendations of the Manten et al. review have not been implemented by the studies [26]. Ethnicity was only documented explicitly in 6 of the 14 studies – and mostly involved Caucasian subjects [31–33,37,39,40]. Not documenting ethnicity leads to difficulties in interpreting the results, as Lp(a) levels vary according to ethnicity [56–58]. Plasma concentration of Lp(a) has been shown to be twice as high in African-American patients compared to white Americans, with the distribution in a bell-shaped frequency (African-Americans) – as opposed to strongly skewed toward low levels, as seen in white American populations [59]. Performing the rest of the studies in Caucasian populations leads to difficulties in generalizing the data to the population as a whole.

In only four of the 14 studies was an apo(a)-independent method of assaying Lp(a) used [31,32,37,39]. Various different assays are available to measure Lp(a) concentrations [including enzyme-linked immunosorbent assay (ELISA), nephelometry and immunoturbidimetry] but not all methods take into account the size of the apo(a) isoform – thus rendering analysis inaccurate [60]. Given that apo(a)-dependent forms of measurement may cause over- or under-estimations of Lp(a) concentrations, the methodologies of these studies are sub-optimal. In only 3 of the 14 studies were attempts made to identify apo(a) isoforms [32,37,39]. Given the fact that the smaller the apo(a) isoform, the higher the concentration of Lp(a), not commenting on whether the nature of the apo(a) isoforms were different between study and control groups represents a potential hidden source of bias in the other studies [27–31,33–36,38,40].

Conclusion

This review demonstrates that there is still no clear role of Lp(a) in either normal or complicated pregnancies. The studies analyzed in this review provide differing accounts, based likely in part due to differing methodologies, with no consensus trend. Therefore – as with previous reviews, no conclusion can be reached as to the definitive role of Lp(a) in pregnancy. However, multiple studies indicate that there may be a role for Lp(a) in pathological processes in pregnancy and in pregnancy outcomes. Further studies are needed of more uniform methodology – preferably involving larger sample size, ethnically diverse populations, identifying apo(a) isoforms and using apo(a)-independent assays. In addition, work in the laboratory should focus on identifying possible mechanisms.

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