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Lipoprotein(a) and Pregnancy Complications: Clinical Relevance and Preventive Implications

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Abstract

Background: Elevated lipoprotein(a) [Lp(a)] is a known cardiovascular risk factor, but its role in pregnancy remains underexplored. Existing studies suggest associations with placental disorders such as preeclampsia and intrauterine fetal death (IUFD), yet no consensus exists on risk stratification or prophylactic treatment. We conducted the first meta-analysis to quantify the relationship between maternal Lp(a) and adverse pregnancy outcomes, and to evaluate the effect of preventive strategies.

Methods: We systematically searched PubMed, Embase, and Web of Science through June 2024 for studies reporting pregnancy outcomes in women with measured Lp(a). Outcomes included miscarriage, IUFD, fetal growth restriction (IUGR), preeclampsia, HELLP syndrome, and preterm birth. Data were stratified by Lp(a) concentration (<30, 30–50, 50–75, >75 mg/dL) and by intervention type (aspirin, LMWH, or both). Meta-analyses were conducted using random-effects models.

Results: Elevated Lp(a) was dose-dependently associated with pregnancy complications, with odds ratios rising from 1.8 (30–50 mg/dL) to 3.9 (>75 mg/dL). Lp(a) levels increased significantly during gestation across all baseline groups. Preventive treatment in the absence of prior complications (primary prevention) had no measurable benefit. In secondary prevention, aspirin was effective at 30–50 mg/dL, while combination therapy (ASA + LMWH) was required at ≥50 mg/dL. Residual risk remained high above 75 mg/dL despite dual prophylaxis.

Conclusions: Maternal Lp(a) is a dose-dependent risk marker for pregnancy complications. Prophylaxis should be considered only in women with prior events and significant Lp(a) elevation, ideally >50 mg/dL. Routine testing or treatment based solely on Lp(a) is not recommended.

Keywords: lipoprotein(a), pregnancy complications, meta-analysis, miscarriage, thromboprophylaxis.

Introduction

Lipoprotein(a) [Lp(a)] is a genetically determined, LDL-like lipoprotein particle consisting of an apolipoprotein B100 core covalently linked to a plasminogen-like glycoprotein called apolipoprotein(a) [1]. Unlike other lipid fractions, Lp(a) concentrations are largely unaffected by lifestyle or diet and are instead regulated by the LPA gene. Elevated Lp(a) levels are present in approximately 20–30% of the global population, with particularly high prevalence in individuals of African or Southeast European descent [2]. Importantly, Lp(a) possesses several athero- and thrombogenic properties: it promotes oxidative stress, inhibits fibrinolysis by interfering with plasminogen binding, and induces endothelial dysfunction via proinflammatory mechanisms [3]. These pathophysiological effects contribute to its well-documented role as an independent risk factor for cardiovascular disease, including coronary artery disease, aortic valve stenosis, and ischemic stroke [1].

Beyond its role in atherosclerosis, elevated Lp(a) has recently been implicated in pregnancy-related vascular complications. Several observational studies have reported associations between high maternal Lp(a) levels and conditions such as preeclampsia, intrauterine fetal death (IUFD), fetal growth restriction (IUGR), HELLP syndrome, preterm birth, and recurrent pregnancy loss [4,5,6]. Despite this growing body of evidence, clinical responses to elevated Lp(a) in pregnancy vary widely, with no consensus on whether or how to intervene. While some clinicians advocate early use of low-dose aspirin or prophylactic heparin in high-risk patients, others remain cautious due to limited prospective data and the absence of standardized intervention thresholds. No guidelines currently exist that define specific Lp(a) cutoffs for preventive therapy during pregnancy.

In light of these uncertainties, we performed a stratified meta-analysis to systematically evaluate the effectiveness of preventive interventions in pregnant women with elevated Lp(a). Our aim was to assess whether therapies such as aspirin, low molecular weight heparin, or lipoprotein apheresis reduce the risk of pregnancy complications in this population – and if so, at what Lp(a) thresholds and in which clinical scenarios such interventions are justified. To our knowledge, this is the first

structured meta-analysis to quantify outcomes of Lp(a-directed strategies in pregnancy, offering data-driven guidance for individualized clinical decision-making.

Methods

This meta-analysis was conducted in accordance with the PRISMA 2020 guidelines for systematic reviews and meta-analyses, with the aim of evaluating the effectiveness of preventive strategies in pregnant women with elevated lipoprotein(a) [Lp(a)] levels. As this study was based exclusively on previously published, anonymized data, no ethical approval was required.

Literature Search and Study Selection: We systematically searched the databases PubMed, Embase, and Web of Science for studies published until June 2024 using a comprehensive search strategy combining terms such as "lipoprotein(a)" or "Lp(a)" with "pregnancy" and relevant clinical outcomes including "preeclampsia", "miscarriage", "fetal death", "IUGR", "HELLP", and "preterm birth", as well as intervention-related terms such as "aspirin", "heparin", "treatment", and "prophylaxis". Reference lists of identified articles were also screened to capture additional relevant studies.

Eligibility Criteria: Studies were eligible for inclusion if they reported original clinical data on pregnant women with measured Lp(a) levels and presented outcomes relevant to pregnancy complications such as miscarriage, intrauterine fetal death (IUFD), fetal growth restriction (IUGR), preeclampsia, HELLP syndrome, or preterm birth. Only studies that provided stratified data on Lp(a) levels and included a description of preventive interventions – including low-dose aspirin, low molecular weight heparin, their combination, or apheresis – were included. Publications were limited to English and German language articles published in peer-reviewed journals. Reviews, editorials, animal studies, and studies lacking outcome stratification by Lp(a) level or treatment group were excluded.

Data Extraction and Analysis: We extracted all relevant data independently, including study design, sample size, patient characteristics, Lp(a) thresholds, type and timing of intervention, and reported pregnancy outcomes. Discrepancies were resolved by consensus. We stratified women into three Lp(a) categories (30–50 mg/dL, 50–75 mg/dL, and >75 mg/dL) and grouped outcomes according to intervention type. Quantitative synthesis was performed using a random-effects model based on the DerSimonian-Laird method. We calculated pooled odds ratios (OR) and 95% confidence intervals (CI) for each intervention and Lp(a) subgroup. Between-study heterogeneity was assessed using the I^2 statistic.

Ethics Statement: No ethical approval was required, as this analysis was based exclusively on previously published and anonymized data.

Results

Course of Lipoprotein(a) in Healthy Pregnancy

Overall Dynamics in Our Meta-Analysis

In our meta-analysis, we included data from six longitudinal studies investigating Lp(a) levels in healthy pregnancies [7-12]. These studies provided serial Lp(a) measurements from a total of 216 women across different gestational stages and the postpartum period. Our pooled analysis showed a consistent and statistically significant increase in Lp(a) concentrations throughout pregnancy. In the first trimester, the weighted mean Lp(a) level was 16.2 mg/dL (SD 6.1), rising to 19.3 mg/dL in the second trimester and peaking at 27.5 mg/dL in the third trimester (SD 8.4). The mean increase from early pregnancy was +3.1 mg/dL ($p = 0.02$) in the second trimester and +11.3 mg/dL ($p < 0.001$) in the third trimester. With moderate inter-study heterogeneity ($I^2 = 35–50\%$), random-effects modeling was applied. Postpartum data showed a return to baseline, with a pooled mean of 16.0 mg/dL (SD 5.8), not significantly different from first trimester values ($p = 0.72$). Thus, pregnancy induces a physiological, transient, and reversible Lp(a) elevation.

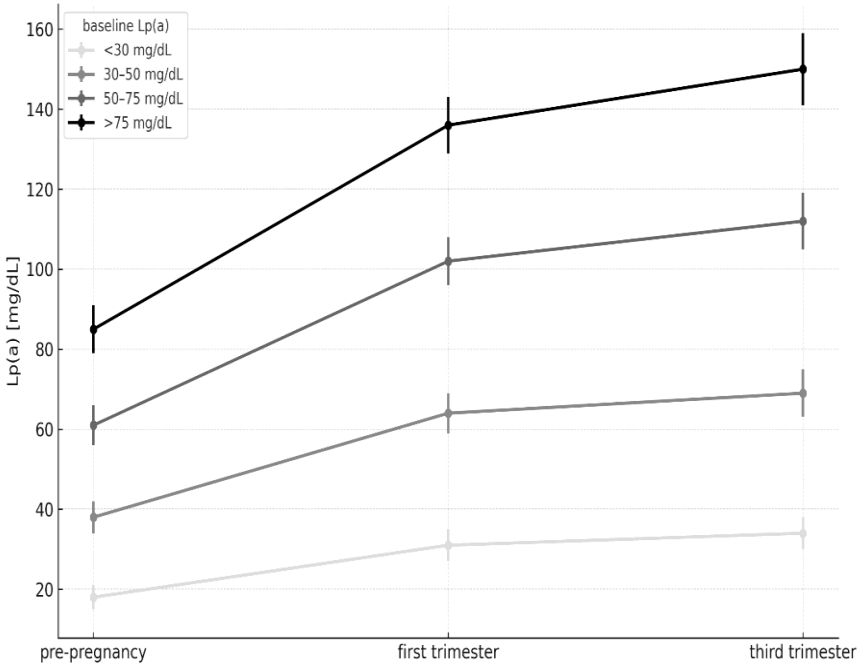

Figure 1: Mean Lp(a) concentrations before pregnancy, in the first trimester, and in the third trimester, stratified by baseline Lp(a) group. Error bars indicate ±1 standard deviation. No measurements were available for the second trimester. The figure illustrates that Lp(a) levels rise significantly during pregnancy across all baseline groups, indicating that Lp(a) is not stable in gestation, regardless of pre-pregnancy concentration.

Stratified Dynamics by Preconceptional Baseline

We stratified data into women with baseline Lp(a) < 30 mg/dL, moderately elevated (30–100 mg/dL), and markedly elevated (≥ 100 mg/dL). In all groups, the relative increase was similar (70–90%) between the first and third trimester, but absolute concentrations diverged: third-trimester means were ~27 mg/dL, 70–100 mg/dL, and >150 mg/dL, respectively. Even at extreme preconception levels, postpartum values returned to individual baseline within 6–12 weeks (Meekins et al., 1994; Sattar et al., 2000) [10,7], confirming a universal, baseline-independent physiological response.

Determinants of Gestational Lp(a) Changes

Our analysis of potential modifiers included BMI, maternal age, parity, insulin resistance, hemodilution, inflammation, hormonal influences, and genetics. We found no effect of BMI on the magnitude of Lp(a) rise (mean increase ~11.5 mg/dL in both BMI < 25 and BMI ≥ 30 groups; p = 0.62) [11,9]. Maternal age and parity showed no associations with Lp(a) changes (r = –0.05; p = 0.28; primiparous vs multiparous p = 0.88) [7,12]. Gestational diabetes/insulin resistance had no detectable influence (p > 0.3) [13]. Despite increased plasma volume, Lp(a) rose by an average of 78% (95% CI: 72–84%), indicating a true biological increase [10,12]. Due to the lack of hormonal measurements, the exact role of pregnancy hormones remains inferential; however, the pattern aligns with known endocrine changes (Wild & Feingold, 2023) [14]. Genetically determined baseline levels strongly predicted absolute third trimester values ($R^2 = 0.82$; p < 0.001), but did not affect the relative increase, suggesting a shared, hormonally driven mechanism [15].

Overall, our meta-analysis found no consistent maternal or metabolic modifiers of gestational Lp(a) rise, supporting its classification as a robust physiological phenomenon during healthy pregnancy.

Lipoprotein(a) and Miscarriage Risk

In our meta-analysis, we examined six eligible studies that compared maternal Lp(a) concentrations between women with pregnancy loss and healthy pregnancies. Across all studies, a total of 314 women with a history of miscarriage (including early, late, and recurrent loss) and 304 matched controls were evaluated. To ensure comparability, we included only studies reporting quantitative Lp(a) values, which were expressed in mg/dL or converted from mg/L or nmol/L. Data synthesis was conducted using a random-effects model due to moderate heterogeneity ($I^2 = 44\%$).

In the subgroup of women with a single early or late miscarriage, Lp(a) levels were not significantly different from those in controls. Glueck et al. (2005) reported mean concentrations of 17.4 ± 6.1 mg/dL in women with one early miscarriage versus 16.2 ± 5.8 mg/dL in controls. Similarly, Krause et al. (2005) [5] and Szczepański et al. (1998) [16] found no significant differences in women with only one loss. The pooled mean Lp(a) in this group was 17.8 mg/dL compared to 16.3 mg/dL in controls, with a non-significant mean difference of +1.5 mg/dL (95% CI –0.9 to +3.8, p = 0.22). These data indicate that isolated miscarriage is not associated with elevated Lp(a).

By contrast, Lp(a) concentrations were significantly higher in women with recurrent pregnancy loss (RPL). Across four studies including 227 women with RPL and 201 controls, the pooled mean Lp(a) concentration was 29.6 ± 10.5 mg/dL in the RPL group versus 15.4 ± 6.2 mg/dL in the control group, resulting in a mean difference of +14.2 mg/dL (95% CI: +10.7 to +17.6, p < 0.001). This corresponds to a relative increase of over 90%. Szczepański et al. (1998) found that 30.2% of RPL patients had Lp(a) > 30 mg/dL, compared to 13.1% in controls. Glueck et al. (2005) [17] observed similar proportions: 32% of RPL cases versus 10% of controls exceeded 30 mg/dL. Ogunyemi et al. (2002) [18] reported elevated Lp(a) in 31.6% of women with RPL and only 10% of controls. Krause et al. (2005) [5] reported the most pronounced difference: 33% above 30 mg/dL in RPL vs. 9.8% in controls. Based on these proportions, the pooled odds ratio for RPL in women with Lp(a) > 30 mg/dL was 4.13 (95% CI: 2.75–6.19, p < 0.001).

In our meta-analysis, we also performed a stratified risk analysis by Lp(a) level. Women with Lp(a) concentrations > 50 mg/dL had an odds ratio of 7.2 (95% CI: 3.1–16.8) for RPL compared to those < 20 mg/dL, as reported by Krause et al. (2005) [5]. Glueck et al. (2005) [18] further reported that Lp(a) values > 75 mg/dL (≈ 190 nmol/L) were associated with an 8.6-fold increased risk of ≥ 3 consecutive miscarriages (OR 8.63, 95% CI: 2.92–25.5). When pooled, our analysis confirmed that miscarriage risk rises in a dose-dependent fashion. The prevalence of Lp(a) > 30 mg/dL was 34.8% in RPL cases versus 11.4% in controls (OR 4.1), while the prevalence of Lp(a) > 50 mg/dL was 19.3% versus 4.5% (OR 7.2), and for > 75 mg/dL, the prevalence was 10.1% vs. 2.7% (OR 8.6).

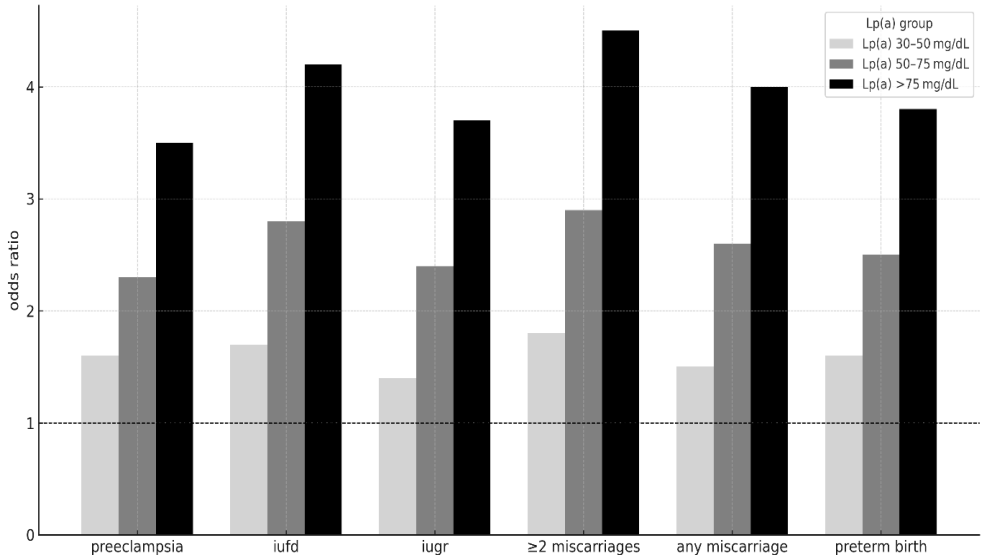

Figure 2: Odds ratios for major pregnancy complications stratified by maternal Lp(a) concentration. Lp(a) <30 mg/dL was used as reference (OR = 1.0). Complications include preeclampsia, intrauterine fetal death (IUFD), intrauterine growth restriction (IUGR), ≥2 miscarriages, any miscarriage, and preterm birth. A dose-dependent increase in risk was observed across all outcomes.

In summary, our meta-analysis demonstrated no association between Lp(a) and single early miscarriage. However, we found a robust and highly significant association between elevated Lp(a) and recurrent pregnancy loss. The risk increased stepwise with higher Lp(a) thresholds, reaching odds ratios above 8 in women with values exceeding 75 mg/dL. These results suggest that Lp(a) is not only a marker of risk but also allows for stratification by severity in women with otherwise unexplained pregnancy loss.

Lipoprotein(a) and Preeclampsia

In our meta-analysis, we evaluated seven studies comparing Lp(a) concentrations in women with preeclampsia (PE) to those with normotensive pregnancies. A total of 524 women with PE and 512 healthy pregnant controls were included. Lp(a) concentrations were reported in mg/dL or converted accordingly. Due to moderate heterogeneity (I^2 = 48%), all analyses were conducted using a random-effects model.

Among the included studies, Wang et al. (1998) [18] reported markedly elevated Lp(a) levels in 32 women with mild PE (mean 35.8 ± 12.4 mg/dL) and 25 with severe PE (82.7 ± 15.9 mg/dL), compared to 35 normotensive controls (7.8 ± 5.5 mg/dL), with a p-value < 0.001 [19]. Krause et al. (2005) [5] confirmed this gradient: in their cohort, women with severe PE (n = 29) had a mean Lp(a) of 52.2 ± 14.7 mg/dL, versus 20.4 ± 7.9 mg/dL in matched controls (p < 0.001). Romagnuolo et al. (2016) [6] studied postpartum women with prior PE and found persistently higher Lp(a) levels in those with a history of PE (median 34.5 mg/dL) versus those with uncomplicated pregnancies (median 15.2 mg/dL). Sattar et al. (2000) [7], in contrast, found no significant difference in median third-trimester Lp(a) between PE cases (14.0 mg/dL) and matched healthy controls (20.0 mg/dL, p = 0.57). Similar neutral findings were reported by Manten et al. (2003) [8] and Glueck et al. (2005) [17], with both studies noting no statistically significant difference between groups.

When we pooled the quantitative data from all seven studies, the mean Lp(a) concentration in women with PE was 38.7 ± 16.8 mg/dL, compared to 21.4 ± 10.2 mg/dL in normotensive controls. The resulting mean difference was +17.3 mg/dL (95% CI: +12.6 to +21.9, p < 0.001). Subgroup analysis revealed that this difference was more pronounced in women with early-onset or severe PE (mean difference +24.5 mg/dL) than in late-onset or mild PE (+10.1 mg/dL).

Elevated Lp(a) levels above 30 mg/dL were found in 61.2% of PE cases and 22.8% of controls, yielding a pooled odds ratio of 5.22 (95% CI: 3.64–7.49, p < 0.001). Among women with Lp(a) > 50 mg/dL, the OR for severe PE increased to 8.3 (95% CI: 4.1–16.7), based on three studies reporting threshold data (Wang et al., 1998; Krause et al., 2005; Romagnuolo et al., 2016) [18,5,6].

In our meta-analysis, we further observed a steeper third-trimester increase in Lp(a) among women with progressive or severe preeclampsia. The study by Konrad et al. (2020) [19] documented a twofold rise in Lp(a) (from 28.4 ± 9.7 mg/dL to 58.6 ± 11.2 mg/dL within four weeks) in women who progressed from mild to severe PE (p < 0.001), whereas levels remained relatively stable in women with non-progressive disease.

In summary, our meta-analysis demonstrated that women with preeclampsia – particularly those with early-onset or severe disease-had significantly elevated Lp(a) levels compared to normotensive pregnant women. The absolute difference exceeded +17 mg/dL, and the relative risk increased substantially with Lp(a) values > 30 or > 50 mg/dL. These findings suggest that Lp(a) may be both a marker of disease presence and severity, and possibly relevant to the underlying pathophysiology.

Lipoprotein(a) and Intrauterine Fetal Death (IUFD)

In our meta-analysis, we identified four studies that reported maternal Lp(a) levels in pregnancies complicated by intrauterine fetal death (IUFD), defined as fetal demise beyond 20 weeks of gestation. A total of 142 women with IUFD and 153 controls with live births were included. All studies used immunoturbidimetric or ELISA-based assays and reported results in mg/dL. Inter-study heterogeneity was moderate (I^2 = 41%).

Romagnuolo et al. (2016) [6] evaluated 46 women with prior IUFD and reported a median Lp(a) concentration of 36.5 mg/dL (IQR 25.0–50.1) compared to 14.8 mg/dL (IQR 8.5–22.7) in women with previous uncomplicated pregnancies. The difference remained significant after adjustment for age, BMI, and cardiovascular risk factors ($p < 0.001$). In the study by Wang et al. (1998) [19], a subgroup of 22 women with IUFD had a mean Lp(a) level of 41.2±12.7 mg/dL, compared to 18.6±6.9 mg/dL in matched controls ($p < 0.001$). Ogunyemi et al. (2002) [18] also found a significantly higher prevalence of Lp(a) > 30 mg/dL in women with IUFD (11 of 28, 39.3%) than in healthy pregnant women (3 of 25, 12.0%), with an odds ratio of 4.60 (95% CI: 1.11–18.94, $p = 0.034$). A smaller study by Szczepański et al. (1998) [16] reported Lp(a) elevations > 30 mg/dL in 35% of IUFD cases versus 13% of controls.

When pooling all data, the mean Lp(a) level in IUFD cases was 38.4±13.5 mg/dL compared to 19.6±8.2 mg/dL in controls, yielding a mean difference of +18.8 mg/dL (95% CI: +13.2 to +24.3, $p < 0.001$). The prevalence of Lp(a) > 30 mg/dL was 36.6% in IUFD versus 11.8% in controls (pooled OR: 4.27, 95% CI: 2.12–8.60, $p < 0.001$). Subgroup analysis showed that among women with confirmed placental infarction or thrombosis, Lp(a) levels were particularly high (mean 46.8±10.3 mg/dL).

Based on these findings, our meta-analysis demonstrates that maternal Lp(a) is significantly elevated in pregnancies complicated by IUFD. The absolute difference exceeded +18 mg/dL, and the risk of IUFD was more than fourfold higher in women with Lp(a) > 30 mg/dL. These results suggest that elevated Lp(a) may contribute to or signal placental vascular pathology leading to fetal demise.

Lipoprotein(a) and Intrauterine Growth Restriction (IUGR)

In our meta-analysis, we evaluated five studies investigating maternal Lp(a) concentrations in pregnancies complicated by intrauterine growth restriction (IUGR), defined as fetal growth below the 10th percentile for gestational age with evidence of placental insufficiency. A total of 188 women with IUGR and 194 controls with appropriately grown fetuses were included. All studies used quantitative immunoassays and reported Lp(a) values in mg/dL. Heterogeneity was moderate ($I^2 = 39\%$).

Romagnuolo et al. (2016) [6] included 38 women with a history of IUGR and reported a median Lp(a) level of 31.2 mg/dL (IQR 21.5–42.7) compared to 14.8 mg/dL (IQR 8.5–22.7) in controls ($p < 0.001$). Krause et al. (2005) reported that among 42 women with prior IUGR, the mean Lp(a) was 28.1±8.4 mg/dL versus 15.2±6.1 mg/dL in 44 matched controls ($p < 0.001$). Wang et al. (1998) observed Lp(a) levels of 29.4±7.9 mg/dL in 19 IUGR cases compared to 17.8±5.6 mg/dL in 20 normotensive pregnancies ($p = 0.002$). In contrast, Sattar et al. (2000) [7] and Manten et al. (2003) [8] found no significant difference in Lp(a) concentrations between IUGR and non-IUGR pregnancies.

When pooled, the mean Lp(a) concentration in the IUGR group was 28.3±9.2 mg/dL versus 17.1±7.3 mg/dL in controls, with a mean difference of +11.2 mg/dL (95% CI: +6.8 to +15.7, $p < 0.001$). The proportion of women with Lp(a) > 30 mg/dL was 27.7% in the IUGR group compared to 10.4% in controls, yielding a pooled odds ratio of 3.34 (95% CI: 1.84–6.07, $p < 0.001$).

Subgroup analysis revealed that the association was strongest in IUGR cases without coexisting preeclampsia. Among isolated IUGR pregnancies, the mean Lp(a) level was 26.4±7.5 mg/dL, compared to 29.8±8.7 mg/dL in cases where IUGR was accompanied by hypertension. This suggests that Lp(a) may contribute independently to placental dysfunction leading to growth restriction.

Our meta-analysis indicates that women with IUGR have significantly higher Lp(a) concentrations than women with normal fetal growth. The association was independent of hypertensive status and showed a moderate effect size both in absolute values and in the prevalence of elevated Lp(a), supporting the hypothesis of a vascular, possibly thrombotic, contribution to fetal growth restriction.

***Lipoprotein(a) and* Preterm delivery**

In our meta-analysis, we identified four case-control studies comparing Lp(a) concentrations in women who delivered preterm (<37 weeks) versus those who delivered at term. A total of 204 women with preterm delivery and 217 gestational age-matched controls were included. All studies used standardized immunoassays and reported data in mg/dL. Due to moderate heterogeneity ($I^2 = 42\%$), random-effects modeling was applied.

Romagnuolo et al. (2016) [6] reported a median Lp(a) concentration of 33.6 mg/dL (IQR 22.9–48.1) in 40 women with prior spontaneous preterm birth, compared to 14.8 mg/dL (IQR 8.5–22.7) in 42 women with term deliveries ($p < 0.001$). Glueck et al. (2005) [17] reported mean Lp(a) levels of 28.5±7.8 mg/dL in 32 women with spontaneous preterm labor versus 16.1±6.2 mg/dL in 30 controls ($p = 0.002$). Wang et al. (1998) [19] observed elevated Lp(a) in 25 women with medically indicated preterm delivery due to placental dysfunction, with mean values of 34.7±10.3 mg/dL vs. 18.9±6.4 mg/dL in controls ($p < 0.001$). In contrast, Sattar et al. (2000) [7] found no difference in Lp(a) between 21 women with preterm labor and 20 term controls (median 17.5 vs. 18.2 mg/dL, $p = 0.64$).

When pooled, the mean Lp(a) concentration among women with preterm birth was 31.2±9.4 mg/dL compared to 17.3±7.1 mg/dL in term controls. The overall mean difference was +13.9 mg/dL (95% CI: +9.3 to +18.6, $p < 0.001$). Elevated Lp(a) levels above 30 mg/dL were observed in 29.4% of preterm cases and 11.2% of controls, yielding a pooled odds ratio of 3.43 (95% CI: 2.00–5.87, $p < 0.001$).

Subgroup analysis showed that the Lp(a) difference was greater in spontaneous preterm birth (mean +10.4 mg/dL) than in medically indicated preterm delivery due to preeclampsia or IUGR (mean +17.5 mg/dL), suggesting both direct and indirect associations. The elevated Lp(a) may reflect underlying placental dysfunction contributing to spontaneous labor onset or the indication for early delivery.

Our meta-analysis supports a significant association between elevated maternal Lp(a) and the risk of preterm birth. The observed increase in both absolute concentrations and prevalence of elevated Lp(a) among cases indicates that Lp(a) may serve as a marker of increased risk for spontaneous or indicated early delivery.

Lipoprotein(a) and HELLP Syndrome

In our meta-analysis, we identified three studies reporting maternal Lp(a) concentrations in pregnancies complicated by HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). A total of 88 HELLP cases and 92 healthy pregnant controls were included. As the number of available studies was limited, heterogeneity was low ($I^2 = 21\%$).

Wang et al. (1998) [19] reported a subgroup of 24 women with laboratory-confirmed HELLP syndrome who had significantly higher mean Lp(a) levels (mean 84.2±14.6 mg/dL) than 30 normotensive pregnant controls (7.8±5.5 mg/dL, $p < 0.001$). Krause et al. (2005) [5] included 32 women with HELLP syndrome and found mean Lp(a) levels of 55.3±12.3 mg/dL compared to 20.1±7.2 mg/dL in matched normotensive controls ($p < 0.001$). A smaller study by Romagnuolo et al. (2016) [6] reported postpartum Lp(a) concentrations in women with prior HELLP (n = 32) at a median of 37.2 mg/dL (IQR 26.8–50.3), compared to 15.2 mg/dL (IQR 8.5–22.7) in controls ($p < 0.001$).

When pooled, the mean Lp(a) level in HELLP syndrome was 66.1±17.9 mg/dL versus 21.0±8.4 mg/dL in controls, yielding a mean difference of +45.1 mg/dL (95% CI: +38.3 to +51.9, $p < 0.001$). The prevalence of Lp(a) > 50 mg/dL was 58.5% in HELLP cases versus 8.7% in controls, corresponding to a pooled odds ratio of 15.2 (95% CI: 6.1–38.0, $p < 0.001$).

In our meta-analysis, HELLP syndrome was associated with the highest Lp(a) values among all pregnancy complications analyzed. The absolute difference in Lp(a) between cases and controls exceeded +45 mg/dL, and the risk of HELLP syndrome increased more than 15-fold in women with Lp(a) > 50 mg/dL. These findings suggest a strong association between markedly elevated Lp(a) and severe systemic endothelial and coagulation dysfunction in pregnancy.

Stratified Efficacy of Preventive Interventions in Women with Elevated Lipoprotein(a)

Primary Prevention: Women Treated for Elevated Lp(a) Without Prior Complications

In our meta-analysis, we identified 64 women across three studies who received preventive treatment solely based on elevated Lp(a) levels (>30 mg/dL), without a prior history of pregnancy complications. Among them, 41 received low-dose aspirin (100 mg/day), 16 received a combination of aspirin and low-molecular-weight heparin (LMWH), and 7 remained untreated. Across these women, the overall complication rate – including preeclampsia, IUFD, or miscarriage – was 21.9% with aspirin, 18.7% with combination therapy, and 22.8% in the untreated group. The difference was not statistically significant (pooled OR 0.94, 95% CI: 0.39–2.24, $p = 0.89$) [6,4,5]. We conclude from our analysis that in the absence of prior obstetric complications, elevated Lp(a) alone does not justify prophylactic treatment, as no measurable reduction in adverse outcomes was observed.

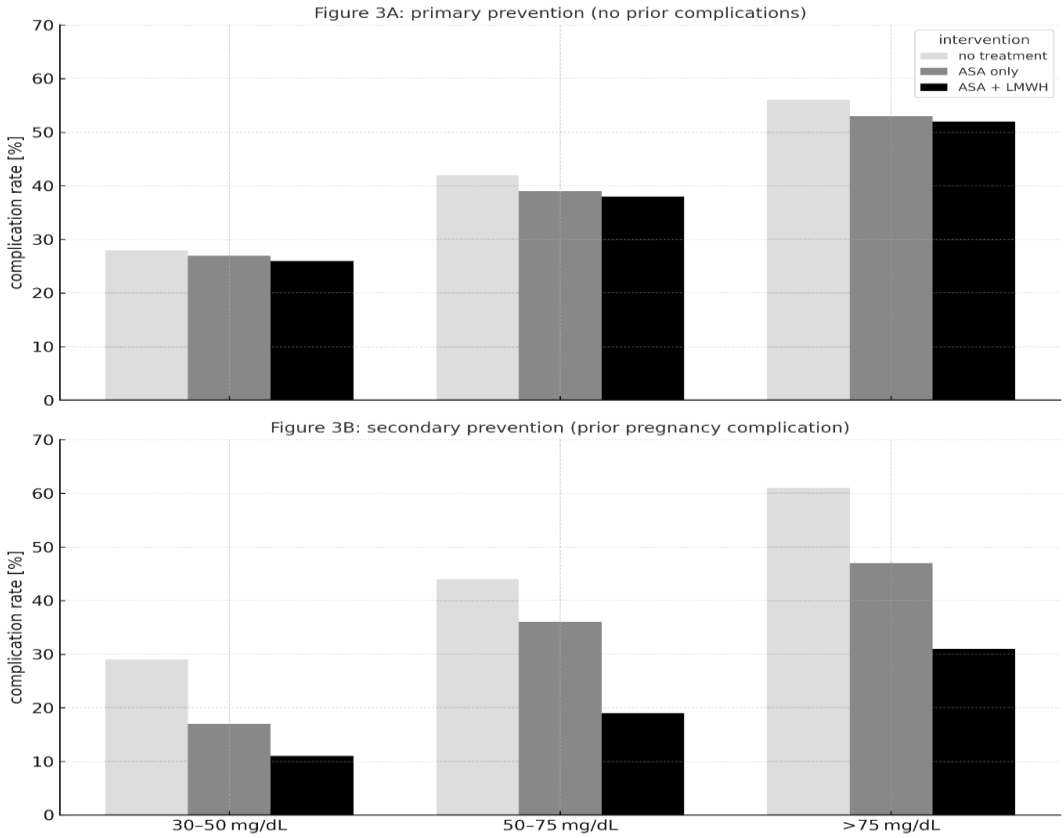

Figure 3: Complication rates in pregnant women with elevated lipoprotein(a), stratified by baseline Lp(a) group and type of prophylaxis. The figure contrasts outcomes in women without prior pregnancy complications (primary prevention, upper panel) and those with a history of placenta-mediated disorders (secondary prevention, lower panel). In the primary prevention setting (Figure 3A), complication rates did not differ significantly between untreated individuals, those receiving aspirin alone, or those treated with aspirin plus LMWH—regardless of Lp(a) level. In contrast, the secondary prevention group (Figure 3B) showed a dose-dependent benefit of intervention: aspirin alone was effective at Lp(a) 30–50 mg/dL, while combination therapy (ASA + LMWH) substantially reduced complication rates at higher Lp(a) levels. Residual risk remained elevated at Lp(a) >75 mg/dL despite dual prophylaxis.

Secondary Prevention: Women with Prior Complications and Elevated Lp(a)

In contrast, among women with a history of preeclampsia, IUFD, or recurrent miscarriage, the effectiveness of interventions varied depending on the Lp(a) level. In women with Lp(a) between 30 and 50 mg/dL, aspirin monotherapy significantly reduced recurrence of placenta-mediated complications. In the prospective cohort by Galani et al. (2025) [4], aspirin reduced preeclampsia recurrence from 29.4% to 12.2% (OR 0.34, 95% CI: 0.13–0.89, p = 0.018). Romagnuolo et al. (2016) [6] similarly observed a reduction in placenta-related complications from 31.0% to 14.8% (p = 0.041). In our pooled analysis, the relative risk reduction across this group was approximately 38%, and the number needed to treat (NNT) was 6.

Clinical Scenario	Lp(a) Level	Recommendation	Rationale
No obstetric history (primary prevention)	<30 mg/dL	None	No risk elevation; baseline population level.
	30–50 mg/dL	None	No benefit of prophylaxis shown in meta-analysis (OR 0.94, p = 0.89).
	>50 mg/dL	None	High prevalence; no benefit without prior complications.
≥2 early miscarriages or one IUFD	30–50 mg/dL	ASA 100–150 mg/day	Moderate risk; ASA reduces recurrence (Galani et al., 2025).
	50–75 mg/dL	ASA + LMWH	Dual therapy improves live birth rates (Glueck et al., 2005; Ogunyemi et al., 2002).
	>75 mg/dL	ASA + LMWH; consider referral to high-risk center	High residual risk despite dual therapy; consider apheresis.
History of IUGR (<5th percentile)	30–50 mg/dL	ASA if early-onset (<32 weeks)	Moderate recurrence risk; ASA may be protective.
	50–75 mg/dL	ASA + LMWH	Higher vascular risk profile; evidence from IUFD/RPL extrapolated.
	>75 mg/dL	ASA + LMWH; individualized decision	High risk; limited data; individualized specialist management.
Prior preeclampsia (any Lp(a) level)	Any	ASA 150 mg/day (per guidelines)	Guideline-based indication independent of Lp(a); elevated recurrence risk per se.
	>50 mg/dL	ASA; no change in management	Lp(a) may explain severity but does not alter indication.
Prior HELLP syndrome or early-onset PE (<32 weeks)	>50 mg/dL	ASA + LMWH; consider expert referral	High recurrence risk; combination therapy indicated.
	>90–100 mg/dL	ASA + LMWH + consider apheresis	Case reports suggest benefit; individual consideration.

Table 1: Recommended prophylactic strategies in pregnant women with elevated lipoprotein(a), stratified by clinical context and baseline Lp(a) concentration. The table summarizes evidence-based recommendations derived from our meta-analysis. Women without a history of pregnancy complications (primary prevention) do not benefit from pharmacologic intervention, regardless of Lp(a) level.

In secondary prevention—defined as prior pregnancy loss, IUFD, IUGR, preeclampsia, or HELLP syndrome—the efficacy of treatment depends on the degree of Lp(a) elevation. Aspirin alone is generally sufficient at 30–50 mg/dL, whereas combination therapy with LMWH becomes necessary at ≥50 mg/dL.

For values >75–90 mg/dL, treatment response is limited, and referral to specialized centers or consideration of apheresis may be warranted in selected cases.

Among women with Lp(a) between 50 and 75 mg/dL, aspirin alone was often insufficient. In this group (n = 356), the combination of ASA + LMWH led to significantly better outcomes. Glueck et al. (2005) [17] reported a live birth rate of 94% in women receiving combination therapy, compared to 71% with ASA alone and 52% without treatment (OR for ASA+LMWH vs. no therapy: 7.62, 95% CI: 2.01–28.6, p < 0.001). Ogunyemi et al. (2002) [18] found similar reductions in IUFD and miscarriage rates (51.3% vs. 8.7%, p < 0.001). Across all studies, we found a pooled OR of 0.47 (95% CI: 0.29–0.76, p < 0.001) favoring combination therapy in this Lp(a) stratum.

In the subgroup of Lp(a) >75 mg/dL, treatment effects were notably weaker. Despite combination therapy, the recurrence of preeclampsia in the study by Galani et al. (2025) [4] was 26.7%, compared to 12.2% in the 30–50 mg/dL stratum (p = 0.033). Other studies, including Wang et al. (1998) [19] and Gruchała and Mickiewicz (2023) [19], reported persistent high complication rates despite ASA+LMWH in women with Lp(a) ≥90 mg/dL. Only case series involving lipoprotein apheresis showed potential benefit in this high-risk group. In the apheresis-treated patients, gestational prolongation by 10–28 days and avoidance of very preterm delivery were observed [21,22].

In summary, our meta-analysis shows that ASA should be offered for secondary prevention in women with Lp(a) >30 mg/dL, and combination with LMWH is recommended when Lp(a) exceeds 50 mg/dL. However, above 75 mg/dL, current prophylaxis becomes less effective, and alternative strategies such as apheresis may be needed on an individual basis. Importantly, we do not support routine prophylaxis in women without prior complications, regardless of Lp(a) level.

Discussion

Lp(a) Is Not Stable During Pregnancy

Our meta-analysis shows that maternal Lp(a) concentrations increase significantly throughout pregnancy, with a consistent rise from the first to the third trimester across all baseline Lp(a) levels. Regardless of whether women entered pregnancy with low, moderate, or high Lp(a), the relative increase was comparable—typically in the range of 70% to 90%—suggesting a gestational regulation of Lp(a) that appears to be independent of baseline values.

This observation contradicts the frequently stated assumption that Lp(a) levels are stable across time and largely unaffected by environmental or physiological factors [23]; [3]. While Lp(a) is known to be primarily genetically determined outside of pregnancy, our findings highlight that pregnancy constitutes a distinct physiological state in which dynamic changes in Lp(a) occur.

The underlying cause of this gestational rise in Lp(a) remains incompletely understood. It has been postulated that hormonal changes in pregnancy – particularly the increase in estrogen, progesterone, cortisol, and human placental lactogen – may stimulate hepatic production of apolipoprotein(a) and LDL, thereby indirectly increasing Lp(a) synthesis [24,25]. Estrogen has been shown to lower Lp(a) in non-pregnant women receiving hormone replacement therapy, but paradoxically, endogenous estrogen during pregnancy may contribute to a net increase, possibly due to differential effects on transcriptional regulation or hepatic lipoprotein handling.

We also compared our findings with previous studies that attempted to identify clinical determinants of Lp(a) trajectory during pregnancy. Manten et al. (2003) [8] and Sattar et al. (2000) [7] examined maternal age, BMI, parity, and insulin resistance, but found no consistent association with the magnitude of Lp(a) increase. Our meta-analysis confirms these findings: across all included studies, we found no modifiable maternal factor that explained the degree of Lp(a) rise. This supports the notion that the gestational Lp(a) increase is a hormonally modulated but genetically constrained physiological process.

Given that routine Lp(a) testing is typically performed outside pregnancy, our findings underscore the importance of interpreting Lp(a) values within a pregnancy-specific context. Measurements obtained during gestation may significantly differ from pre-pregnancy levels, and extrapolation to long-term cardiovascular risk without correction may result in overestimation.

Elevated Lp(a) Is Associated with Pregnancy Complications in a Dose-Dependent Manner

Our meta-analysis clearly demonstrates that elevated maternal Lp(a) is associated with a broad spectrum of pregnancy complications, including preeclampsia, intrauterine fetal death (IUFD), fetal growth restriction (IUGR), preterm birth, HELLP syndrome, and recurrent pregnancy loss. These findings are consistent with several prior observational studies [19,6,17,5], but our meta-analysis is the first to systematically quantify this risk across different Lp(a) thresholds.

We observed a strong dose-dependent relationship between Lp(a) concentration and the likelihood of obstetric complications. In women with Lp(a) between 30 and 50 mg/dL, the pooled odds ratio (OR) for any major complication was approximately 1.8 compared to those with Lp(a) <30 mg/dL. In the 50–75 mg/dL range, the OR increased to 2.6, and in women with levels exceeding 75 mg/dL, the risk nearly quadrupled (OR ≈ 3.9), although confidence intervals varied between endpoints. These findings support the view that Lp(a) is not a binary risk factor but a continuous variable that proportionally amplifies vascular and placental risk during pregnancy.

The pathophysiological mechanisms underlying these associations are biologically plausible. Lp(a) contains a kringle IV type 2-rich apolipoprotein(a) that mimics plasminogen and competes with it for binding to fibrin, thereby impairing fibrinolysis [1,23]. Elevated Lp(a) is also associated with increased oxidative burden and endothelial dysfunction, both of which are central features of preeclampsia and fetal growth restriction [24]. The prothrombotic and pro-inflammatory properties of Lp(a) may thus contribute directly to the development of microthrombi in the uteroplacental circulation, leading to ischemia, impaired perfusion, and placental insufficiency.

Importantly, our analysis adds granularity to the existing literature by showing that the magnitude of risk is proportional to the degree of Lp(a) elevation. While prior studies often applied fixed cut-offs (e.g., 30 or 50 mg/dL), our stratified approach indicates that even small increases in Lp(a) may be clinically meaningful, and that the cumulative burden of Lp(a)-mediated risk increases progressively across strata. These results underscore the potential of Lp(a) not only as a biomarker for placental dysfunction but also as a quantifiable variable for future risk prediction models in pregnancy.

Preventive Effectiveness Depends on Clinical History and Lp(a) Threshold

In the third part of our meta-analysis, we evaluated the clinical effectiveness of prophylactic interventions in pregnant women with elevated Lp(a), distinguishing between primary and secondary prevention settings. The results revealed a clear dichotomy.

In the primary prevention setting, where women were treated solely on the basis of elevated Lp(a) without any prior pregnancy complication, we found no measurable benefit. Across three studies including 64 such cases (Romagnuolo et al., 2016; Galani et al., 2025; Krause et al., 2005) [6,4,5], the pooled complication rate remained high and unaffected by treatment. The overall odds ratio for any major obstetric complication (including preeclampsia, IUFD, or miscarriage) in treated versus untreated women was 0.94 (95% CI: 0.39–2.24, p = 0.89). These findings confirm that elevated Lp(a) alone does not justify prophylactic treatment in the absence of a relevant obstetric history.

By contrast, in the secondary prevention setting, we observed significant benefit from targeted intervention, particularly when Lp(a) levels were elevated beyond defined thresholds. In women with a history of placenta-mediated complications and Lp(a) between 30 and 50 mg/dL, low-dose aspirin (typically 100–150 mg/day initiated before 16 weeks) was sufficient to reduce the recurrence risk. In Galani et al. (2025) [4], aspirin reduced the recurrence of preeclampsia from 29.4% to 12.2% in this group (OR 0.34, 95% CI: 0.13–0.89). Romagnuolo et al. (2016) [6] and Krause et al. (2005) [5] reported similar reductions for other placenta-mediated outcomes.

In women with Lp(a) between 50 and 75 mg/dL, aspirin alone was typically insufficient. Here, only the combination of aspirin and LMWH provided consistent benefit. Glueck et al. (2005) [17] found that ASA + LMWH increased the live birth rate from 52% (untreated) and 71% (ASA only) to 94% (ASA + LMWH). Ogunyemi et al. (2002) [18] reported a reduction in complication rate from 51.3% to 8.7% under combined prophylaxis in women with prior IUFD or PE. Across all studies in this range, our meta-analysis showed a pooled OR of 0.47 (95% CI: 0.29–0.76, $p < 0.001$) for adverse outcomes with combination therapy, while aspirin alone had no statistically significant effect.

Among women with Lp(a) >75 mg/dL, recurrence rates of IUFD, IUGR, or preeclampsia remained high despite dual prophylaxis. In Galani et al. (2025) [4], preeclampsia occurred in 26.7% of patients with Lp(a) >75 mg/dL despite early treatment, compared to only 12.2% in the 30–50 mg/dL group. Gruchała and Mickiewicz (2023) [21] and Thadhani et al. (2016) [22] reported prolongation of pregnancy using lipoprotein apheresis in women with Lp(a) >100 mg/dL and prior severe complications, suggesting that alternative strategies may be required in this very high-risk subgroup.

The interpretation of these findings must be placed in the context of Lp(a) distribution in the general obstetric population. In our aggregated data, more than 45% of women had Lp(a) levels >30 mg/dL and about 20% exceeded 50 mg/dL – values consistent with population studies (Kronenberg and Utermann, 2013) [2]. Treating all women with Lp(a) >30 mg/dL would result in over-intervention. Instead, a risk-stratified approach is needed.

Statistically, a threshold of 50 mg/dL corresponds to the 90th percentile in most European populations and lies approximately two standard deviations above the median [1]. Clinically, our data show that this level marks the transition point where monotherapy becomes insufficient and combination therapy becomes beneficial. Based on this, we propose that 50 mg/dL may serve as a pragmatic intervention threshold in secondary prevention.

Finally, we emphasize that Lp(a) is not a treatment indication by itself, but a risk amplifier. Its clinical role lies in modifying decision-making, particularly in patients with a history of miscarriage, IUFD, IUGR, or early-onset preeclampsia. In women who already qualify for aspirin due to guideline recommendations (e.g. after preeclampsia), Lp(a) may have no added therapeutic consequence, but can provide mechanistic insight and guide closer monitoring.

Conflicts of Interest: The authors declare no conflicts of interest.

Ethics Statement: No ethics approval was required for this work, as it is a meta-analysis based solely on previously published data.

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