American Journal of Preventive Cardiology 20 (2024) 100885

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

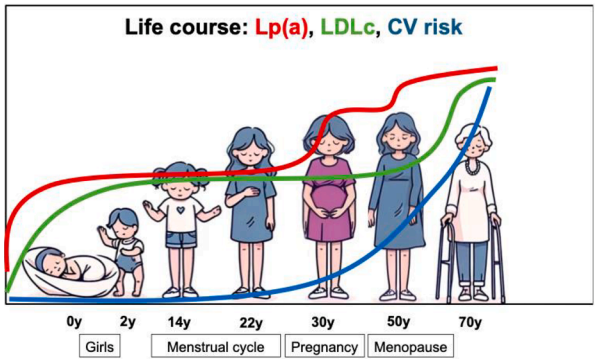
State-of-the-Art Review

Lipoprotein(a) throughout life in women

Pablo Corral [a,*], María Gabriela Matta [a,b], Carlos Aguilar-Salinas [c,d], Roopa Mehta [e], Gabriela Berg [f], Massimiliano Ruscica [g,h], Laura Schreier [f]

[a] FASTA University, Pharmacology and Research Department. Instituto Investigaciones Clínicas (IIC), Mar del Plata, Argentina
[b] Department of Cardiology, Gold Coast University Hospital, Southport, Australia
[c] Unidad de Investigación de Enfermedades Metabólicas. Departamento de Diabetes y Metabolismo. Dirección de Investigación. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, México City, Mexico
[d] Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Beirut, Lebanon
[e] Unidad de Investigación de Enfermedades Metabólicas. Departamento de Diabetes y Metabolismo, México City, Mexico
[f] Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Instituto de Fisiopatología y Bioquímica Clínica (INFIBIOC-UBA), Laboratorio de Lípidos y Aterosclerosis, Buenos Aires, Argentina
[g] Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Università degli Studi di Milano, Milan, Italy
[h] Department of Cardio-Thoracic-Vascular Diseases, Foundation IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milan, Italy

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Lipoprotein(a)
Women
Lipoprotein(a) variability

ABSTRACT

Lipoprotein (a) [Lp(a)] is a lipoprotein with multiple deleterious characteristics and is a recognized cardiovascular (CV) risk factor. The pro-atherogenic, pro-thrombotic, and pro-inflammatory features of Lp(a) are associated not only with atherosclerotic vascular disease but also with aortic valve calcification and all-cause mortality. One of the most interesting aspects of Lp(a) is that its level is determined by genetics in more than 90% of cases, with lifestyle habits having very little influence. Therefore, the recommendation is to test it, at least, once in a lifetime. Contrary to previous beliefs, evidence in recent decades has shown that women have the same or even greater CV risk than men of the same age, attributed to female sex hormones. Different stages of a woman's life can impact on Lp(a) levels,

* Corresponding author.
E-mail address: drpablocorral@gmail.com (P. Corral).

https://doi.org/10.1016/j.ajpc.2024.100885
Received 10 May 2024; Received in revised form 25 September 2024; Accepted 15 October 2024
Available online 29 October 2024

from newborn to menopause, including other critical moments such as menarche and pregnancy. The main objective of this review is to describe and analyze the effect of different specific periods of a woman's life on Lp(a) levels and the potential clinical relevance on their CV risk.

1. Introduction

Lipoprotein(a) [Lp(a)] is a cardiovascular (CV) risk factor first described in 1963 by Berg K [1]. This lipoprotein has several characteristics that explain its role as a risk factor, such as its proatherogenic, prothrombotic and pro-inflammatory effects [2]. One of the most intriguing aspects of Lp(a) is its strong genetic influence on its level, as genetics determine approximately 90% of the plasma Lp(a) concentration. Consequently, lifestyle habits have minimal influence on Lp(a) values [3]. Currently, there is no specific or effective pharmacologic treatment to reduce Lp(a) to the levels required to obtain a CV benefit [4]. Given that high levels of this lipoprotein indicate a greater CV risk and that a correct categorization of patients is necessary, global recommendations and guidelines support testing Lp(a) levels, at least, once in a lifetime [5,6]. In this context, there is limited information on how female sex affects major lipids (e.g., post-menopause, women experience a decline in their lipid profile). Despite CV disease being the leading cause of death in women, their CV health is often overlooked [7]. Significant sex disparities exist in managing CV risk factors, with women being less likely than men to receive routine risk factor assessment. Therefore, it is crucial to understand sex differences in CV health metrics to better implement solutions and optimize care [8]. Considering that Lp(a) concentrations are ≥ 90% genetically determined and 17% higher in post-menopausal women than in men [9], the primary objective of this review is to provide an update on the understanding of the course of Lp(a) in a woman's life and to discuss its potential clinical impact on CV risk.

2. Lp(a) from birth to pre-menarche age

2.1. Lp(a) levels during early life and childhood

Due to the prominent role of genetic factors in determining Lp(a) plasma levels, exposure to this independent CV risk factor starts early on in life [10,11]. Consequently, the pediatric population could be a target for screening and intervention, even though CV events may not occur until the adulthood.

At birth, Lp(a) levels are low and rapidly increase during the first year of life, reaching adult levels by almost age two [12]. As a result, the measurement of Lp(a) is not recommended during this period. In the Copenhagen Baby Heart Study and the COMPARE sub-study, investigators evaluated the development of lipid and lipoprotein concentrations in 450 newborns during the first 14–16 months of life [12,13]. They confirmed that Lp(a) levels increased in a stepwise manner from birth. Mean Lp(a) levels were 2.2 (95% CI, 1.9–2.5), 2.4 (2.0–2.7), 4.1 (3.4–4.9), and 14.6 (11.4–17.9) mg/dL in cord blood, neonatal venous samples, and at 2 and 15 months, respectively. The concentration at 15 months was comparable to parental levels [12]. Levels were not associated with sex or weight at birth, although gestational age has been reported as a covariate in other studies [14]. High levels of Lp(a) at birth were associated with higher concentrations at 14–16 months of age [15]. Due to the strong correlation between umbilical cord, newborn and adult concentrations, the authors suggest that there is an opportunity for using cord samples for lipid screening, to detect those individuals who will have high Lp(a) later in life. Finally, in infants with levels ≥ 90th percentile, 75% had one parent with elevated Lp(a) (>42 mg/dL or 88 nmol/L), suggesting that reverse cascade screening may also be possible. Unfortunately, the mechanisms that explain the increment of Lp(a) early on in life have not been systematically studied. Potential mediators include the incremental effect of growth hormone and adaptation to inflammatory or dietary factors [16]. One of the drawbacks of this analysis was the under representation of different ethnic groups. Other publications examining cord blood levels confirm the influence of racial background on Lp(a) concentrations [12,17,18]. In a study from Singapore, the Lp(a) levels in cord blood were measured in ethnic Indians, Malays and Chinese, and these were correlated with the coronary risk of the respective population. Investigators stated that newborn concentrations mirror adult Lp(a) levels according to ethnicity and coronary risk.

In children, Lp(a) has been measured in several cohorts: follow-up data from the Cardiovascular Risk in Young Finns Study (YFS), initiated in the 1970s-1980s confirms that the Lp(a) levels in childhood remain the same over the years. Individuals with Lp(a) >30 mg/dL continued to have high levels, reaffirming the relative stability of levels from an early age [19]. This contrasts with findings from a large pediatric cohort (n=2740) from the Netherlands; here, researchers reported that Lp(a) levels increased during childhood (after age 8), the majority of participants (68%) showing intra-individual variation of at least 20% between two measurements (i.e. levels increased into adulthood). In this publication, authors suggest that levels do vary during childhood and therefore single measurements may not be accurate [20]. The clinical impact of such variability is unknown at present and may not be significant for those with high Lp(a) concentrations.

2.2. Elevated Lp(a) and cardiovascular risk in childhood

Elevated Lp(a) in children has been associated with an increased risk of premature CV disease and a greater risk of CV outcomes in family members [21]. Recently, researchers of the YFS evaluated the association between Lp(a) measured in childhood and the occurrence of CV events in adults [22,23]. There were 95 cases and 3596 non-cases, with the median age of diagnosis being 47 years. They showed that a Lp(a) >30 mg/dL in youth was associated with a 2 times great risk for CV events [HR 1.96 (95% CI: 1.35–2.57)] in adulthood. These results were replicated in the Bogalusa Heart Study where children and adolescents aged 8–17 years who had high concentrations of Lp(a) had 2.5 times the risk for CV disease compared to a similar group with low Lp(a) (15 cases and 572 non cases) [23]. Interestingly, there was no association between youth Lp(a) levels and carotid intima media thickness in either cohort.

The Bogalusa Heart study also looked at the association between childhood Lp(a) and the risk of myocardial infarction in parents [24]. In this study, evaluating 2438 children (8–17 years old) from a biracial community (black-white), Lp(a) levels tended to decrease in younger children, specifically those aged 8–10 years, and to increase in older children, particularly those aged 11–17 years. However, although factors such as sexual maturation, assessed by Tanner stage, and sex were independently related to Lp(a) levels, their contribution was not significant. Other covariates such as age, subscapular skinfold thickness (as a measure of adiposity), cigarette smoking, oral contraceptive use, and alcohol consumption did not contribute to the variation of Lp(a) levels [24]. Additionally, among Caucasians those aged 8–17 years, who had a parent with myocardial infarction (n=90) had increased levels of Lp(a) compared to those children without (Lp(a) 22.4 versus 17.1 mg/dl, $p<0.01$). An NHANES analysis confirmed these findings in Hispanic children, showing a strong association between Lp(a) >30 mg/dL and parental history of premature heart disease (<50 years) [25].

In a cohort of Kuwaiti Arab adolescents (316 males 458 females) aged 10–19 years, it was observed that boys had exhibited significantly elevated levels of apolipoprotein (apo) B concentrations compared to the girls. However, Lp(a) levels were greater in girls. Among the

overweight and obese participants, there was a tendency to present increased levels of LDL, and apoB, but not Lp(a). Additionally, the stratification by age of 14 did not appear to affect Lp(a) levels [26].

The association between Lp(a) and stroke is not as consistent as that between Lp(a) and coronary heart disease [27]. Studies on childhood strokes, evaluating the role of Lp(a) in pediatric stroke, have provided insights into the potential pathogenic mechanisms of this lipoprotein.

Childhood arterial ischemic strokes are unusual and can be associated with risk factors such as cardiopulmonary diseases, inflammatory disorders, genetic mutations, connective tissue disorders, and thrombophilia [28]. Elevated Lp(a) >30 mg/dl was significantly associated with ischemic stroke in two case-control studies, including recurrent stroke [29,30] ([OR: 2.5, 95% CI (1.1–6.2), p< 0.05] and [OR: 4.3 (1.3–14.4), p= 0.03], respectively. Sultan et al, carried out a meta-analysis, including 16 observational studies in children with stroke: they confirmed a positive association between elevated lipoprotein (a) >30 mg/dL and stroke [OR 4.24 (2.94–6.11)] [31].

However, the mechanisms involved remain intriguing. Tsimikas proposes that Lp(a) pathogenesis may differ depending on a person's age [32]. He hypothesizes that in pediatric strokes, the antifibrinolytic or pro-inflammatory properties of Lp(a) may predominate, whereas in older adults, the typical proatherogenic properties of Lp(a) together with traditional risk factors come into play causing strokes. A recent study looking at Kaiser Permanente data, appears to support his idea; the researchers found that atherosclerosis was rare in persons <20 years (2%) and increased to 42.5% in the 40–49-year-old age group [33].

In summary, research suggests that Lp(a) levels reach adult levels by the neonatal period, though recent studies indicate some variability during childhood. Elevated Lp(a) in childhood might be a causal risk factor for pediatric stroke due to its unique properties. Additionally, there do not appear to be significant differences between sexes in these findings.

3. Lp(a) from menarche to pre-menopause

3.1. Trajectory of Lp(a) levels from childhood through adolescence

While guidelines acknowledge sex-specific risk factors and provide general recommendations for lipid management in women [7], information regarding the trajectory of Lp(a) levels accompanying midlife and the menopause transition is limited. Although it is established that genetic variants associated with raised Lp(a) levels determine high levels at birth [34], it appears that Lp(a) concentrations are low early in life and gradually reach adult levels before the first 2 years of life [17]. Results from studies from birth and the first year of life have raised the question of whether Lp(a) testing should be performed in youth, and if so, under what circumstances [35]. First, it will help identify individuals who will develop high concentrations of Lp(a) later in life, and second, it will be possible to identify at least one parent with high Lp(a) through a reverse cascade approach (i.e., child-to-parent cascade). Within this context, adolescent and parental history of premature heart diseases significantly associate with Lp(a) levels in children [25]. Furthermore, in children with familial hypercholesterolemia, elevated Lp(a) is more predictive than the low-density lipoprotein cholesterol (LDL-c) in predicting the early onset of atherosclerotic CV diseases in family members [36]. Early identification of children with a diagnosis of familial hypercholesterolemia could facilitate more aggressive management to reduce the risk of atherosclerotic CV diseases. The hypothesis to assess Lp(a) levels in youth was further supported by the conclusions of the population-based LIFE Child (German civilization diseases cohort) study, demonstrating that in children aged 5–18 years, Lp(a) levels remained stable in 94% of them during repeated measurements (i.e., 1–4 follow-ups, approximately 1 year apart) [37].

3.2. Influence of menstrual cycle and fertility treatments on Lp(a) levels

At the menarche age, Lp(a) levels do not appear to be significantly affected by hormonal changes during the different phases of the menstrual cycle. However, this relationship is lost when progesterone is present at supraphysiological concentrations. These conclusions stem from a study that evaluated Lp(a) changes during physiological menstrual cycle and in women undergoing ovarian stimulation with recombinant follicle stimulating hormone (FSH) [38]. Trying to summarize data linking fertility therapy with subsequent cardiovascular outcomes, a meta-analysis showed that among 41,910 women who received fertility therapy and 1400,202 women who did not, there was no increased risk of a cardiac event, or diabetes mellitus. Conversely, there was a trend toward higher risk of stroke [39]. However, it should be recall that among 2496,441 individuals, women who gave birth after assisted reproductive technologies were not at increased risk of CVD over a median follow-up of 11 years compared with those who conceived without assisted reproductive technologies [40].

Specifically, Lp(a) levels only increased during the luteal phase upon FSH administration, returning to the baseline levels if pregnancy did not occur. Interestingly, Lp(a) concentrations increased only when progesterone levels rose, with no changes even when very high concentrations of estrogen were present. Therefore, it could be stated that from menarche and during the reproductive age -except pregnancy- Lp(a) remains stable until perimenopause [41].

4. Lp(a) and pregnancy

4.1. Hormonal changes and lipid metabolism during pregnancy

During pregnancy, women undergo physiological adaptations essential for supporting adequate fetal growth and development [42]. Significant hormonal shifts occur compared to non-pregnant women. The levels of leptin and insulin notably increase in pregnant women, leading to peripheral insulin resistance and consequent alterations in lipid metabolism [43,44]. Most pregnant women experience increases in total cholesterol, triglycerides, high-density lipoprotein (HDLc), LDLc, and Lp(a), with the most pronounced changes occurring during the third trimester. It is generally accepted that maternal triglycerides increase three to four times during normal pregnancy compared to pre-pregnancy values, and HDL rises by approximately 30% [45–47]. Lp(a) levels are known to approximately double during pregnancy, but the underlying mechanisms remain partially understood [48]. Theories suggest that estrogen may affect Lp(a) synthesis and clearance, Lp(a) could function as an acute phase protein in response to endothelial damage, or it may play a role in placental development [49–51].

4.2. Impact of elevated Lp(a) on pregnancy complications and long-term CV risk

These lipid changes are critical for ensuring a steady nutrient supply to the fetus despite variable maternal food intake. However, disruptions in lipid metabolism during pregnancy can heighten the risk of cardiovascular disease and complications such as preeclampsia, gestational diabetes mellitus (GDM), intrauterine growth restriction, and premature birth [52–55]. Approximately 20–30% of the general population has elevated Lp(a) levels. Given this prevalence, it is anticipated that a similar proportion of pregnant women will also have elevated Lp(a). This widespread occurrence implies that elevated Lp(a) could potentially influence pregnancy outcomes, increasing the risk of complications such as preeclampsia, diabetes, preterm delivery, and low birth weight [56]. Such conditions not only pose short-term risks of maternal and fetal morbidity and mortality but also elevate the long-term risk of CV events such as myocardial infarction, stroke, and heart failure [57]. Moreover, a history of pregnancy complications is recognized as a risk-enhancing factor for CV disease in the guidelines of the American

Heart Association/American Stroke Association [58,59].

Pre-eclampsia, affecting 2–8% of pregnancies, is linked to increased lipid oxidation products and reduced antioxidant levels, with endothelial cell injury playing a crucial role [60–62]. Various predisposing factors, such as maternal age, obesity, diabetes, and chronic hypertension, have been associated with the increased prevalence of pre-eclampsia [63,64]. Several biomarkers for early diagnosis and screening have been investigated, including those representing angiogenic and antiangiogenic factors, inflammation, oxidative stress, endothelial damage, endocrine hormones, lipid metabolism, homeostasis, and fetal distress [65]. Despite extensive research, only the placental growth factor is widely accepted as a reliable biomarker for early diagnosis [66,67]. The similarity between the pathogenesis of pre-eclampsia and atherosclerosis, along with the antifibrinolytic properties of Lp(a), has prompted researchers to examine the role of Lp(a) in pre-eclampsia [68]. While investigations elucidating the relationship between Lp(a) and pre-eclampsia have produced varied outcomes, with some studies reporting null associations and others suggesting elevated Lp(a) levels [68,69]. Additionally, differences in preeclampsia severity, such as more extensive endothelial damage in severe cases, may lead to the consumption of Lp(a) as an acute-phase protein and introduce pitfalls in comparisons. Moreover, differences in study designs, small sample sizes, variations in trimester measurements, and demographic characteristics further complicate interpretation, thereby impeding comprehensive meta-analytical synthesis [68,69].

Genetic variations in LPA may also influence inflammatory responses and the risk of preeclampsia, with an Lp(a) cutoff value of >52.5 mg/dL suggested as an indicator of severity [70,71].

Gestational diabetes mellitus (GDM), which affects 5–25% of pregnant women globally, is associated with risks such as hypertensive disorders, preterm delivery, and post-pregnancy type 2 diabetes. While various risk factors for GDM are well-recognized, the relationship between GDM and Lp(a) remains underexplored [72]. Despite evaluating multiple risk factors and markers in women with GDM, few studies have explored the relationship between GDM and Lp(a). Interestingly, contrary to the findings of multiple studies that have shown associations between low Lp(a) levels and incident type 2 diabetes mellitus, the observation in pregnant women is the opposite [73,74]. Yue et al. [75] demonstrated that Lp(a) levels measured at 24–28 weeks were significantly increased and independently associated with the odds of GDM. Recently, Chen et al. [76] investigated the association between Lp(a) levels during early pregnancy and GDM risk in 445 pregnant women at 12–14 gestational weeks from the "Maternal Key Nutritional Factors and Offspring's Atopic Dermatitis" study. Their findings revealed a notable elevation in Lp(a) levels among pregnant women diagnosed with GDM compared to those without the condition. Even after adjusting for covariates such as age and gestational weeks, Lp(a) remained significantly linked to GDM risk [OR (95%CI) = 1.21 (1.08–1.36) per 10 mg/L, $p<0.05$].

Despite existing knowledge gaps, early identification of elevated Lp(a) levels holds promise for predicting and managing potential complications, leading to better outcomes for both mother and child. Recent Polish guidelines on dyslipidemia management in pregnant patients emphasize evaluating Lp(a) levels alongside other lipid parameters before pregnancy [77]. Although routine screening during pregnancy is not recommended, recent research suggests that incorporating non fasting lipid screening into first trimester exams could improve the diagnosis of lipid disorders [78].

Future research should focus on elucidating the mechanisms behind elevated Lp(a) levels during pregnancy and their impact on complications like preeclampsia and GDM. Longitudinal studies are needed to assess the long-term cardiovascular effects of elevated Lp(a) and pregnancy-related complications. Investigating genetic variations in LPA could offer insights into personalized prevention and treatment strategies. Additionally, integrating Lp(a) screening into prenatal care and evaluating its effectiveness in managing pregnancy-related complications could be beneficial.

5. Lp(a) from the menopausal transition to the postmenopause

5.1. Effects of menopause on Lp(a) levels and CV risk

Even though more than 90% of the circulating Lp(a) level is genetically determined there are other conditions that could influence its variation throughout life, with menopause being the only physiological cause, at least known until now.

Postmenopausal women run the same or even higher risks of coronary heart disease than men. Several factors in the climacteric, such as the loss of endogenous estrogenic protection, the increased prevalence of metabolic syndrome and dyslipidemias, largely explain the high CV risk observed after menopause [79]. However, it is still unclear whether these factors are due to aging, menopausal status, or both. A current report of the Study of Women's Health Across the Nation (SWAN) -a prospective study of menopausal transition in several ethnicities- demonstrated that while increase in blood pressure and weight were consistent with a linear model indicative of chronological aging, LDLc and other lipid markers increase dramatically within the year surrounding the final menstrual period, independent of aging alone or ethnicity [80,81].

It is important to discern whether the proatherogenic changes that appear in middle-aged women are due to the age or to the transition to menopausal state. The action of estrogens on lipid metabolism and plasma profile must be considered [42]. Estrogens regulate the production of messenger RNA (mRNA) for endogenous proteins involved in lipid metabolism in liver cells, mediate the regulation of Sterol regulatory element-binding protein-2 (SREBP-2) expression in hepatocytes [82] and downregulate the proprotein convertase subtilisin/kexin type 9 (PCSK-9), protease which binds to LDL receptors (LDLr) and induces their degradation in hepatocytes [83]. The consequent increase in LDLr allows for greater LDL uptake and lower plasma LDLc levels. Estrogens also increase HDLc levels by reducing hepatic lipase activity, enzyme involved in the HDL catabolism. Consequently, with estrogen fluctuation or even its deficiency in the transition from peri to menopause, LDLc, apoB and triglycerides increase [84,41], and HDLc losses its atheroprotective functions [85,86].

5.2. Role of estrogens and hormone replacement therapy in modulating Lp(a)

Beyond traditional lipid risk factors, with respect to Lp(a), some studies found elevated levels in postmenopausal women [41,87,88]. These references range from showing that in women menopausal status is the strongest independent predictor of Lp(a) levels, increasing from perimenopause to evidence that Lp(a) increases mainly with aging, although a modest further increase was observed in women over 50 years of age compared to men [87–89]. On the other hand, there are other authors who do not detect an increase in Lp(a) or relate it to increasing age [90–92].

In this context of divergences there are interesting reports in favor of the action of estrogens on apo(a) regulation in the liver. Studies carried out in a transgenic mouse model developed by means of human apo(a) yeast artificial chromosome, found that estrogen negatively regulates both plasma Lp(a) level and Lp(a)-induced vascular impact [93,94]. Analysis of liver RNA revealed that estrogens, and tamoxifen also, exert plasma apo(a) lowering effect by regulation of apo(a) mRNA. These findings may explain that with the reduction of estrogen in menopause, the downregulation of apo(a) does not occur.

Oral estrogen replacement therapy makes the lipid profiles favorable, and several studies have assessed hormone effects on Lp(a). Levels of Lp(a) were significantly lower in postmenopausal women under hormone replacement therapy than in those not receiving [95–97]. Recent meta-analysis based on randomized controlled trials

demonstrated that hormone replacement therapy in general, and tibolone in particular, reduced Lp(a) concentration in postmenopausal women 20–25% on average [98,99].

The strong evidence between hormone replacement therapy and Lp (a) contributes to associate the increase in this lipoprotein with the menopausal state, but not to be considered as a therapeutic option to reduce the Lp(a)-associated risk given that there are studies with controversial results [95,100]. In fact, after the Women's Health Initiative (WHI) results, hormone therapy is not recommended for reducing atherosclerotic CV risk. It is also a matter of debate whether there are a consistent association between Lp(a) levels and CV outcomes in postmenopausal women [101]. Cook N et al., evaluating Lp(a) clinical utility in women, found in 3 cohorts from the WHI study, that Lp(a) was associated with CV disease only among those women with high total cholesterol (>220 mg/dL) and improvement of prediction of Lp(a) was minimal [101].

Finally, as it is not fully understood whether the increase in Lp(a) associated with menopause is caused by aging or hormonal changes, more precise and stringent design studies and appropriate covariate adjustments would be needed to elucidate this point. Whether the relationship between the increase in Lp(a) and CV disease in postmenopause is particularly greater or responds to the well-known linear relationship is still mater of discussion. These findings challenge the current recommendation to measure Lp(a) only once in a woman's life, encouraging a reevaluation of Lp(a) levels after menopause, as an Lp (a)>50 mg/dL or >125 nmol/L is undoubtedly a risk factor.

6. Discussion

This review provides a detailed examination of Lp(a) and its significant role in modulating cardiovascular (CV) risk across various life stages in women. Discrepancies in existing data are largely attributed to differences in Lp(a) quantification methods, calibrators, and expression units. Genetic factors predominantly determine Lp(a) levels from birth, which are linked to increased CV disease risks as concentrations escalate. While Lp(a) levels are relatively stable during childhood, they can rise during specific developmental periods, supporting the case for early screening.

Lp(a) levels undergo notable fluctuations from menarche to postmenopause, significantly impacting the CV risk profile in women. During reproductive years, Lp(a) levels generally stabilize but can surge during pregnancy due to hormonal changes, enhancing CV risk. A similar increase occurs postmenopause, driven by hormonal shifts, suggesting a heightened CV risk that surpasses traditional factors.

Premature menarche, polycystic ovarian syndrome, pregnancy loss, premature ovarian failure, and early menopause are reproductive conditions increasingly studied for their associations with cardiovascular risk [102,103]. Elevated Lp(a) levels have been implicated as a risk factor for cardiovascular disease due to their proatherogenic and prothrombotic properties. Investigating the link between these female reproductive disorders and Lp(a) levels could provide insightful data on cardiovascular risk stratification in women, helping to develop targeted interventions that address the specific cardiovascular needs of women experiencing these reproductive health issues [102.103].

7. Conclusion

This review emphasizes that Lp(a) levels are critically influenced by genetics and moderately by lifestyle, affecting CV disease risk throughout a woman's life. It underscores the importance of enhanced understanding and monitoring of Lp(a) at crucial life stages, particularly during pregnancy and menopause, to facilitate more effective prevention and treatment strategies tailored to women's specific CV health needs.

Funding source

The present study has not received any grants or financial support.

Author declaration

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work. [OR] We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated.

CRediT authorship contribution statement

Pablo Corral: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **María Gabriela Matta:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Carlos Aguilar-Salinas:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Roopa Mehta:** Writing – review & editing, Writing – original draft, Data curation. **Gabriela Berg:** Visualization. **Massimiliano Ruscica:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Data curation, Conceptualization. **Laura Schreier:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest concerning the preparation and submission of this manuscript.

References

[1] Berg K, Mohr J. Genetics of the LP system. Acta Genet Stat Med 1963;13:349–60. https://doi.org/10.1159/000151818.
[2] DeFilippis AP, Trainor PJ, Thanassoulis G, Brumback LC, Post WS, Tsai MY, Tsimikas S. Atherothrombotic factors and atherosclerotic cardiovascular events: the multi-ethnic study of atherosclerosis. Eur Heart J 2022;43(10):971–81. https://doi.org/10.1093/eurheartj/ehab600. Mar 7.
[3] Tada H, Yamagami K, Sakata K, Usui S, Kawashiri MA, Takamura M. Healthy lifestyle, lipoprotein(a) levels and the risk of coronary artery disease. Eur. J. Clin. Investig. 2024;54(1):e14093. https://doi.org/10.1111/eci.14093. JanEpub 2023 Sep 15.
[4] Reyes-Soffer G, Yeang C, Michos ED, Boatwright W, Ballantyne CM. High lipoprotein(a): Actionable strategies for risk assessment and mitigation. Am J Prev Cardiol 2024;18:100651. https://doi.org/10.1016/j.ajpc.2024.100651.
[5] Koschinsky ML, Bajaj A, Boffa MB, Dixon DL, Ferdinand KC, Gidding SS, Gill EA, Jacobson TA, Michos ED, Safarova MS, Soffer DE, Taub PR, Wilkinson MJ, Wilson DP, Ballantyne CM. A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice. J Clin Lipidol 2024. https://doi.org/10.1016/j.jacl.2024.03.001. Mar 29:S1933-2874(24)00033-3.
[6] Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, Dweck MR, Koschinsky M, Lambert G, Mach F, McNeal CJ, Moriarty PM, Natarajan P, Nordestgaard BG, Parhofer KG, Virani SS, von Eckardstein A, Watts GF, Stock JK, Ray KK, Tokgözoğlu LS, Catapano AL. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J 2022;43(39):3925–46. https://doi.org/10.1093/eurheartj/ehac361. Oct 14.
[7] Roeters van Lennep JE, Tokgözoğlu LS, Badimon L, Dumanski SM, Gulati M, Hess CN, Holven KB, Kavousi M, Kayıkçıoğlu M, Lutgens E, Michos ED, Prescott E, Stock JK, Tybjaerg-Hansen A, Wermer MJH, Benn M. Women, lipids, and atherosclerotic cardiovascular disease: a call to action from the European Atherosclerosis Society. Eur Heart J 2023;44(39):4157–73. https://doi.org/10.1093/eurheartj/ehad472. Oct 14.

[8] Kaur G, Kobo O, Parwani P, Chieffo A, Gulati M, Mamas MA. Sex differences in Life's Essential Eight and its Association with mortality among US adults without known cardiovascular disease. Am J Prev Cardiol 2024;18:100685. https://doi.org/10.1016/j.ajpc.2024.100685. Jun 3.

[9] Nordestgaard BG, Langsted A. Lipoprotein(a) and cardiovascular disease. Lancet 2024. https://doi.org/10.1016/S0140-6736(24)01308-4. Sep 12:S0140-6736(24)01308-4.

[10] Kronenberg F, Mora S, Stroes ESG. Consensus and guidelines on lipoprotein(a) - seeing the forest through the trees. Curr Opin Lipidol 2022;33(6):342–52. https://doi.org/10.1097/MOL.0000000000000855. Dec 1Epub 2022 Oct 14.

[11] Wilson DP, Koschinsky ML, Moriarty PM. Expert position statements: comparison of recommendations for the care of adults and youth with elevated lipoprotein(a). Curr Opin Endocrinol Diabetes Obes 2021;28(2):159–73. https://doi.org/10.1097/MED.0000000000000624. Apr 1.

[12] Strandkjær N, Hansen MK, Nielsen ST, Frikke-Schmidt R, Tybjærg-Hansen A, Nordestgaard BG, Tabor A, Bundgaard H, Iversen K, Kamstrup PR. Lipoprotein(a) levels at birth and in early childhood: the compare study. J Clin Endocrinol Metab 2022;107(2):324–35. https://doi.org/10.1210/clinem/dgab734. Jan 18.

[13] Taageby Nielsen S, Mohr Lytsen R, Strandkjær N, Juul Rasmussen I, Sillesen AS, Vøgg ROB, Axelsson Raja A, Nordestgaard BG, Kamstrup PR, Iversen K, Bundgaard H, Tybjærg-Hansen A, Frikke-Schmidt R. Significance of lipids, lipoproteins, and apolipoproteins during the first 14-16 months of life. Eur Heart J 2023;44(42):4408–18. https://doi.org/10.1093/eurheartj/ehad547. Nov 7.

[14] Low PS, Heng CK, Saha N, Tay JS. Racial variation of cord plasma lipoprotein(a) levels in relation to coronary risk level: a study in three ethnic groups in Singapore. Pediatr Res 1996;40:718–22. https://doi.org/10.1203/00006450-199611000-00011.

[15] Holven KB. Plasma cholesterol levels in infancy: a neglected resource. Eur Heart J 2023;44(42):4419–21. https://doi.org/10.1093/eurheartj/ehad558. Nov 7.

[16] Coassin S, Kronenberg F. Lipoprotein(a) beyond the kringle IV repeat polymorphism: The complexity of genetic variation in the LPA gene. Atherosclerosis 2022;349:17–35. https://doi.org/10.1016/j.atherosclerosis.2022.04.003. May.

[17] Rifai N, Heiss G, Doetsch K. Lipoprotein(a) at birth, in blacks and whites. Atherosclerosis 1992;92(2-3):123–9. https://doi.org/10.1016/0021-9150(92)90271-h. Feb.

[18] Kwiterovich Jr PO, Virgil DG, Garrett ES, Otvos J, Driggers R, Blakemore K, Cockrill SL, Macfarlane RD. Lipoprotein heterogeneity at birth: influence of gestational age and race on lipoprotein subclasses and Lp(a)lipoprotein. Ethn Dis. 2004;14(3):351–9. Summer.

[19] Raitakari O, Kivelä A, Pahkala K, Rovio S, Mykkänen J, Ahola-Olli A, Loo BM, Lyytikäinen LP, Lehtimäki T, Kähönen M, Juonala M, Rönnemaa T, Lamina C, Kronenberg F, Viikari J. Long-term tracking and population characteristics of lipoprotein(a)in the cardiovascular risk in Young Finns study. Atherosclerosis 2022;356:18–27. https://doi.org/10.1016/j.atherosclerosis.2022.07.009. Sep.

[20] de Boer LM, Hof MH, Wiegman A, Stroobants AK, Kastelein JJP, Hutten BA. Lipoprotein(a) levels from childhood to adulthood: Data in nearly 3,000 children who visited a pediatric lipid clinic. Atherosclerosis 2022;349:227–32. https://doi.org/10.1016/j.atherosclerosis.2022.03.004. May.

[21] Genovesi S, Giussani M, Lieti G, Orlando A, Patti I, Parati G. Evidence and uncertainties on lipoprotein(a) as a marker of cardiovascular health risk in children and adolescents. Biomedicines 2023;11(6):1661. https://doi.org/10.3390/biomedicines11061661. Jun 8.

[22] Masson W, Barbagelata L, Corral P, Nogueira JP. Association between lipid markers in childhood/adolescence and cardiovascular events in adulthood: A systematic review. Arch Argent Pediatr 2024;122(2):e202310094. https://doi.org/10.5546/aap.2023-10094.eng. Apr 1.

[23] Raitakari O, Kartiosuo N, Pahkala K, Hutri-Kähönen N, Bazzano LA, Chen W, Urbina EM, Jacobs Jr DR, Sinaiko A, Steinberger J, Burns T, Daniels SR, Venn A, Woo JG, Dwyer T, Juonala M, Viikari J. Lipoprotein(a) in youth and prediction of major cardiovascular outcomes in adulthood. Circulation 2023;147(1):23–31. https://doi.org/10.1161/CIRCULATIONAHA.122.060667. Jan 3.

[24] Srinivasan SR, Dahlen GH, Jarpa RA, Webber LS, Berenson GS. Racial (black-white) differences in serum lipoprotein(a) distribution and its relation to parental myocardial infarction in children. Bogalusa Heart Study. Circulation. 1991;84(1):160–7. https://doi.org/10.1161/01.cir.84.1.160. Jul.

[25] Obisesan TO, Aliyu MH, Adediran AS, Bond V, Maxwell CJ, Rotimi CN. Correlates of serum lipoprotein(A) in children and adolescents in the United States. The third National Health Nutrition and Examination Survey (NHANES-III). Lipid Health Dis 2004;3:29. https://doi.org/10.1186/1476-511X-3-29. Dec 16.

[26] Akanji AO, Al-Isa AN, Thalib L. Determinants of blood levels of some thrombogenic biomarkers in healthy Arab adolescent subjects. Clin Chem Lab Med 2011;49(10):1681–90. https://doi.org/10.1515/CCLM.2011.645. Oct.

[27] Langsted A, Nordestgaard BG, Kamstrup PR. Elevated Lipoprotein(a) and Risk of Ischemic Stroke. J Am Coll Cardiol 2019;74(1):54–66. https://doi.org/10.1016/j.jacc.2019.03.524. Jul 9Erratum in: J Am Coll Cardiol. 2020 May 12;75(18):2385.

[28] Torres M, Schenk A. Lipoprotein(a): does it play a role in pediatric ischemic stroke and thrombosis? Curr Atheroscler Rep 2023;25(6):299–307. https://doi.org/10.1007/s11883-023-01102-5. Jun.

[29] Teber S, Deda G, Akar N, Soylu K. Lipoprotein(a) levels in childhood arterial ischemic stroke. Clin Appl Thromb Hemost 2010;16(2):214–7. https://doi.org/10.1177/1076029609334124. Apr.

[30] Sträter R, Vielhaber H, Kassenböhmer R, von Kries R, Göbel U, Nowak-Göttl U. Genetic risk factors of thrombophilia in ischaemic childhood stroke of cardiac origin. A prospective ESPED survey. Eur J Pediatr 1999;158(Suppl 3):S122–5. https://doi.org/10.1007/pl00014336. Dec.

[31] Sultan SM, Schupf N, Dowling MM, Deveber GA, Kirton A, Elkind MS. Review of lipid and lipoprotein(a) abnormalities in childhood arterial ischemic stroke. Int J Stroke 2014;9(1):79–87. https://doi.org/10.1111/ijs.12136. Jan.

[32] Tsimikas S. Elevated lipoprotein(a) and the risk of stroke in children, young adults, and the elderly. Eur Heart J 2021;42(22):2197–200. https://doi.org/10.1093/eurheartj/ehab251. Jun 7.

[33] Poisson SN, Hills NK, Sidney S, Fullerton HJ. Prevalence of atherosclerotic risk factors among children and young adults with arterial ischemic stroke. JAMA Neurol 2022;79(9):901–10. https://doi.org/10.1001/jamaneurol.2022.2077. Sep 1.

[34] Wang XL, Wilcken DE, Dudman NP. Early expression of the apolipoprotein(a) gene: relationships between infants' and their parents' serum apolipoprotein(a) levels. Pediatrics 1992;89(3):401–6. Mar.

[35] Kohn B, Ashraf AP, Wilson DP. Should lipoprotein(a) be measured in youth? J Pediatr 2021;228:285–9. https://doi.org/10.1016/j.jpeds.2020.08.042. Jan.

[36] Zawacki AW, Dodge A, Woo KM, Ralphe JC, Peterson AL. In pediatric familial hypercholesterolemia, lipoprotein(a) is more predictive than LDL-C for early onset of cardiovascular disease in family members. J Clin Lipidol 2018;12(6):1445–51. https://doi.org/10.1016/j.jacl.2018.07.014. Nov-Dec.

[37] Stürzebecher PE, Uttinger KL, Vogel M, Schlingmann M, Ceglarek U, Isermann B, Kiess W, Körner A, Laufs U. Lipoprotein(a) serum concentrations in children in relation to body mass index, age and sex. Pediatr Res 2024. https://doi.org/10.1038/s41390-024-03108-4. Feb 28.

[38] Ricci G, Tamaro G, Simeone R, Giolo E, Nucera G, De Seta F, Guaschino S. Lipoprotein(a) changes during natural menstrual cycle and ovarian stimulation with recombinant and highly purified urinary FSH. Hum Reprod 2001;16(3):449–56. https://doi.org/10.1093/humrep/16.3.449. Mar.

[39] Dayan N, Filion KB, Okano M, Kilmartin C, Reinblatt S, Landry T, Basso O, Udell JA. Cardiovascular risk following fertility therapy: systematic review and meta-analysis. J Am Coll Cardiol 2017;70(10):1203–13. https://doi.org/10.1016/j.jacc.2017.07.753. Sep 5.

[40] Magnus MC, Fraser A, Håberg SE, Rönö K, Romundstad LB, Bergh C, Spangmose AL, Pinborg A, Gissler M, Wennerholm UB, Åsvold BO, Lawlor DA, Opdahl S. Maternal risk of cardiovascular disease after use of assisted reproductive technologies. JAMA Cardiol 2023;8(9):837–45. https://doi.org/10.1001/jamacardio.2023.2324. Sep 1.

[41] Derby CA, Crawford SL, Pasternak RC, Sowers M, Sternfeld B, Matthews KA. Lipid changes during the menopause transition in relation to age and weight: the Study of Women's Health Across the Nation. Am J Epidemiol 2009;169(11):1352–61. https://doi.org/10.1093/aje/kwp043. Jun 1.

[42] Patel N, Mittal N, Wilkinson MJ, Taub PR. Unique features of dyslipidemia in women across a lifetime and a tailored approach to management. Am J Prev Cardiol 2024;18:100666. https://doi.org/10.1016/j.ajpc.2024.100666. Apr 5.

[43] Lain KY, Catalano PM, Weissgerber TL, Wolfe LA. Metabolic changes in pregnancy. Clin Obstet Gynecol 2007;50:938–48. https://doi.org/10.1097/GRF.0b013e31815a5494.

[44] Hodson K, Man CD, Smith FE, Thelwall PE, Cobelli C, Robson SC, Taylor R. Mechanism of insulin resistance in normal pregnancy. Horm Metab Res 2013;45:567–71. https://doi.org/10.1055/s-0033-1337988. 4.

[45] Shaefer-Graf UM, Graf K, Kulbancka I, Jjos SL, Dudenhausen J, Vetter K, Herrera E. Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabet Care 2008;31:1858–63. https://doi.org/10.2337/dc08-0039.

[46] Knopp R, Bonet B, Zhu X-D. Lipid metabolism in pregnancy. In: Cowett R, editor. Principles of perinatal neonatal metabolism. New York: Springer-Verlag; 1998. p. 221–58.

[47] Pusukuru R, Shenoi AS, Kyada PK, Ghodke B, Mehta V, Bhuta K, Bhatia A. Evaluation of Lipid Profile in Second and Third Trimester of Pregnancy. J. Clin. Diagn. Res. 2016;10:QC12–6. https://doi.org/10.7860/JCDR/2016/17598.7436.

[48] Sattar N, Clark P, Greer IA, Shepherd J, Packard CJ. Lipoprotein(a) levels in normal pregnancy and in pregnancy complicated with pre-eclampsia. Atherosclerosis 2000;148:407–11. https://doi.org/10.1016/s0021-9150(99)00296-8.

[49] Wang Q, Wurtz P, Auro K, Makinen VP, Kangas AJ, Soininen P, Tiainen M, Tynkkynen T, Jokelainen J, Santalahti K, et al. Metabolic profiling of pregnancy: cross-sectional and longitudinal evidence. BMC Med 2016;14:205. https://doi.org/10.1186/s12916-016-0733-0.

[50] Manten GT, Franx A, van der Hoek YY, Hameeteman TM, Voorbij HA, Smolders HC, Westers P, Visser GH. Changes of plasma lipoprotein(a) during and after normal pregnancy in Caucasians. J Matern Fetal Neonatal Med 2003;14:91–5. https://doi.org/10.1080/jmf.14.2.91.95.

[51] Zechner R, Desoye G, Schweditsch MO, Pfeiffer KP, Kostner GM. Fluctuations of plasma lipoprotein-A concentrations during pregnancy and post partum. Metabolism 1986;35:333–6. https://doi.org/10.1016/0026-0495(86)90150-2.

[52] Charlton F, Tooher J, Rye KA, Hennessy A. Cardiovascular risk, lipids and pregnancy: preeclampsia and the risk of later life cardiovascular disease. Heart Lung Circ 2014;23:203–12. https://doi.org/10.1016/j.hlc.2013.10.087.

[53] Baumfeld Y, Novack L, Wiznitzer A, Sheiner E, Henkin Y, Sherf M, et al. Pre-Conception Dyslipidemia Is Associated with Development of Preeclampsia and Gestational Diabetes Mellitus. PloS one 2015;10(10):e0139164. https://doi.org/10.1371/journal.pone.0139164. Erratum in: PLoS One. 2015;10(11):e0142462.

[54] Yeboah FA, Ngala RA, Bawah AT, Asare-Anane H, Alidu H, Hamid AM, et al. Adiposity and hyperleptinemia during the first trimester among pregnant women with preeclampsia. Int J Womens Health 2017;9:449–54. https://doi.org/10.2147/IJWH.S134088.

[55] Wang C, Zhu W, Wei Y, Su R, Feng H, Lin L, Yang H. The predictive effects of early pregnancy lipid profiles and fasting glucose on the risk of gestational diabetes mellitus stratified by body mass index. J Diabetes Res 2016:3013567. https://doi.org/10.1155/2016/3013567.
[56] Lewek J, Bielecka-Dąbrowa A, Toth PP, Banach M. Dyslipidemia management in pregnant patients: a 2024 update. Eur Heart J Open 2024. https://doi.org/10.1093/ehjopen/oeae032. April.
[57] Abu-Awwad SA, Craina M, Boscu L, Bernad E, Ciordas PD, Marian C, Iurciuc M, Abu-Awwad A, Iurciuc S, Bernad B, Anastasiu Popov DM, Maghiari AL. Lipid profile variations in pregnancies with and without cardiovascular risk: consequences for both mother and newborn. Children (Basel) 2023;10(9):1521. Sep 7.
[58] Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation 2019;140:e596–646.
[59] Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:1545–88.
[60] Tesfa E, Nibret E, Munshea A. Maternal lipid profile and risk of pre-eclampsia in African pregnant women: a systematic review and meta-analysis. PLoS One 2020; 15(12):e0243538. https://doi.org/10.1371/journal.pone.0243538. Dec 23.
[61] Gupta S, Aziz N, Sekhon L, Agarwal R, Mansour G, Li J, et al. Lipid peroxidation and antioxidant status in preeclampsia a systematic review. Obstet Gynecol Surv 2009;64(11):750–9. https://doi.org/10.1097/OGX.0b013e3181bea0ac. Nov.
[62] Manten GT, Voorbij HA, Hameeteman TM, Visser GH, Franx A. Lipoprotein(a) in pregnancy: a critical review of the literature. Eur J Obstet Gynecol Reprod Biol 2005;122:13–21. https://doi.org/10.1016/j.ejogrb.2005.03.013.
[63] Paré E, Parry S, McElrath TF, Pucci D, Newton A, Lim KH. Clinical risk factors for preeclampsia in the 21st century. Obstet Gynecol 2014;124(4):763–70. https://doi.org/10.1097/AOG.0000000000000451. Oct.
[64] Poon LC, Kametas NA, Chelemen T, Leal A, Nicolaides KH. Maternal risk factors for hypertensive disorders in pregnancy: a multivariate approach. J Hum Hypertens 2010;24(2):104–10. https://doi.org/10.1038/jhh.2009.45. Feb.
[65] Shahid R, Bari MF, Hussain M. Serum biomarkers for the prediction and diagnosis of preeclampsia: a meta-analysis. Original Article. J Taibah Univ Med Sci 2022;17 (1):14–27. https://doi.org/10.1016/j.jtumed.2021.07.003.
[66] De Kat AC, Hirst J, Woodward M, Kennedy S, Peters SA. Prediction models for preeclampsia: a systematic review. Pregnan Hypertens 2019;16:48e66. https://doi.org/10.1016/j.preghy.2019.03.005.
[67] Widmer M, Cuesta C, Khan KS, Conde-Agudelo A, Carroli G, Fusey S, et al. Accuracy of angiogenic biomarkers at < 20 weeks' gestation in predicting the risk of pre-eclampsia: a WHO multicentre study. Pregnan Hypertens 2015;5(4): 330e338. https://doi.org/10.1016/j.preghy.2015.09.004.
[68] Fanshawe AE, Ibrahim M. The current status of lipoprotein(a)in pregnancy: a literature review. J Cardiol. 2013;61(2):99–106. https://doi.org/10.1016/j.jjcc.2012.09.009. Feb.
[69] Manten GT, Voorbij HA, Hameeteman TM, Visser GH, Franx A. Lipoprotein(a) in pregnancy: a critical review of the literature. Eur J Obstet Gynecol Reprod Biol 2005;122:13–21. https://doi.org/10.1016/j.ejogrb.2005.03.013.
[70] Tuten A, Gungor Z, Ekmekci H, Ekmekci OB, Kucur M, Yilmaz N, Donma O, Sonmez H, Acıkgoz A, Madazlı R. Relationship between LPA SNPs and inflammatory burden in patients with preeclampsia to address future cardiovascular risk. J Matern Fetal Neonatal Med 2021;34(6):898–906. https://doi.org/10.1080/14767058.2019.1622667. Mar.
[71] Konrad E, Güralp O, Shaalan W, Elzarkaa AA, Moftah R, Alemam D, Malik E, Soliman AA. Correlation of elevated levels of lipoprotein(a), high-density lipoprotein and low-density lipoprotein with severity of preeclampsia: a prospective longitudinal study. J Obstet Gynaecol 2020;40(1):53–8. https://doi.org/10.1080/01443615.2019.1603214. Jan.
[72] Habibi N, Mousa A, Tay CT, Khomami MB, Patten RK, Andraweera PH, Wassie M, Vandersluys J, Aflatounian A, Bianco-Miotto T, Zhou SJ, Grieger JA. Maternal metabolic factors and the association with gestational diabetes: A systematic review and meta-analysis. Diabetes Metab Res Rev 2022;38(5):e3532. https://doi.org/10.1002/dmrr.3532. Jul.
[73] Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J 2022;43:3925–46. https://doi.org/10.1093/eurheartj/ehac361.
[74] Mora S, Kamstrup PR, Rifai N, et al. Lipoprotein(a) and risk of type 2 diabetes. Clin Chem 2010;56:1252–60. https://doi.org/10.1373/clinchem.2010.146779.
[75] Yue C-Y, Ying C-M. Epidemiological analysis of maternal lipid levels during the second trimester in pregnancy and the risk of adverse pregnancy outcome adjusted by pregnancy BMI. J Clin Lab Anal 2018;32:e22568.
[76] Chen XT, Ye Y, Zhang Y, Jiang Y, Wang Y, Chen HY, Dou YL, Li MR, Sun XP, Yan WL. [Association of lipoprotein a in early pregnancy with gestational diabetes mellitus: a prospective cohort study]. Zhonghua Liu Xing Bing Xue Za Zhi 2021;42(5):903–8. May 10.
[77] Banach M, Burchardt P, Chlebus K, et al. PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021. Arch Med Sci 2021;17(6):1447–547. https://doi.org/10.5114/aoms/141941. Published 2021 Nov 8.
[78] Golwala S, Dolin CD, Nemiroff R, Soffer D, Denduluri S, Jacoby D, Lewey J. Feasibility of lipid screening during first trimester of pregnancy to identify women at risk of severe dyslipidemia. J Am Heart Assoc 2023;12(10):e028626. https://doi.org/10.1161/JAHA.122.028626. May 16.
[79] Torosyan N, Visrodia P, Torbati T, Minissian MB, Shufelt CL. Dyslipidemia in midlife women: approach and considerations during the menopausal transition. Maturitas 2022;166:14–20. https://doi.org/10.1016/j.maturitas.2022.08.001. Dec.
[80] El Khoudary SR, Greendale G, Crawford SL, Avis NE, Brooks MM, Thurston RC, Karvonen-Gutierrez C, Waetjen LE, Matthews K. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). Menopause 2019;26(10):1213–27. https://doi.org/10.1097/GME.0000000000001424. Oct.
[81] Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, Sutton-Tyrrell K. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol 2009;54(25):2366–73. https://doi.org/10.1016/j.jacc.2009.10.009. Dec 15.
[82] Meng Y, Zong L. Estrogen stimulates SREBP2 expression in hepatic cell lines via an estrogen response element in the SREBP2 promoter. Cell Mol Biol Lett 2019; 24:65. https://doi.org/10.1186/s11658-019-0194-5. Dec 3.
[83] Feldman RD. Sex-specific determinants of coronary artery disease and atherosclerotic risk factors: Estrogen and beyond. Can J Cardiol 2020;36(5): 706–11. https://doi.org/10.1016/j.cjca.2020.03.002. May.
[84] Berg G, Mesch V, Boero L, Sayegh F, Prada M, Royer M, Muzzio ML, Schreier L, Siseles N, Benencia H. Lipid and lipoprotein profile in menopausal transition. Effects of hormones, age and fat distribution. Horm Metab Res 2004;36(4): 215–20. https://doi.org/10.1055/s-2004-814450. Apr.
[85] El Khoudary SR, Hutchins PM, Matthews KA, Brooks MM, Orchard TJ, Ronsein GE, Heinecke JW. Cholesterol efflux capacity and subclasses of HDL particles in healthy women transitioning through menopause. J Clin Endocrinol Metab 2016;101(9):3419–28. https://doi.org/10.1210/jc.2016-2144. Sep.
[86] Zago V, Sanguinetti S, Brites F, Berg G, Verona J, Basilio F, Wikinski R, Schreier L. Impaired high density lipoprotein antioxidant activity in healthy postmenopausal women. Atherosclerosis 2004;177(1):203–10. https://doi.org/10.1016/j.atherosclerosis.2004.07.011. Nov.
[87] Slunga L, Asplund K, Johnson O, Dahlén GH. Lipoprotein(a) in a randomly selected 25-64 years old population: the Northern Sweden Monica Study. J Clin Epidemiol 1993;46(7):617–24. https://doi.org/10.1016/0895-4356(93)90034-x. Jul.
[88] Jenner JL, Ordovas JM, Lamon-Fava S, Schaefer MM, Wilson PW, Castelli WP, Schaefer EJ. Effects of age, sex, and menopausal status on plasma lipoprotein(a) levels. The Framingham Offspring Study. Circulation 1993;87(4):1135–41. https://doi.org/10.1161/01.cir.87.4.1135. Apr.
[89] Simony SB, Mortensen MB, Langsted A, Afzal S, Kamstrup PR, Nordestgaard BG. Sex differences of lipoprotein(a) levels and associated risk of morbidity and mortality by age: The Copenhagen General Population Study. Atherosclerosis 2022;355:76–82. https://doi.org/10.1016/j.atherosclerosis.2022.06.1023. Aug.
[90] Akita H, Matsubara M, Shibuya H, Fuda H, Chiba H. Effect of ageing on plasma lipoprotein(a) levels. Ann Clin Biochem 2002;39(Pt 3):237–40. https://doi.org/10.1258/0004563021901937. May.
[91] Lippi G, Targher G, Salvagno GL, Montagnana M, Franchini M, Guidi GC. Lipoprotein(a) and ageing. Clin Lab 2010;56(9-10):463–6.
[92] Zysow BR, Kauser K, Lawn RM, Rubanyi GM. Effects of estrus cycle, ovariectomy, and treatment with estrogen, tamoxifen, and progesterone on apolipoprotein(a) gene expression in transgenic mice. Arterioscler Thromb Vasc Biol 1997;17(9): 1741–5. https://doi.org/10.1161/01.atv.17.9.1741. Sep.
[93] Nakagami F, Nakagami H, Osako MK, Iwabayashi M, Taniyama Y, Doi T, Shimizu H, Shimamura M, Rakugi H, Morishita R. Estrogen attenuates vascular remodeling in Lp(a) transgenic mice. Atherosclerosis 2010;211(1):41–7. https://doi.org/10.1016/j.atherosclerosis.2010.01.016. Jul.
[94] Suk Danik J, Rifai N, Buring JE, Ridker PM. Lipoprotein(a), hormone replacement therapy, and risk of future cardiovascular events. J Am Coll Cardiol 2008;52(2): 124–31. https://doi.org/10.1016/j.jacc.2008.04.009. Jul 8.
[95] Kim CJ, Jang HC, Cho DH, Min YK. Effects of hormone replacement therapy on lipoprotein(a) and lipids in postmenopausal women. Arterioscler Thromb 1994; 14(2):275–81. https://doi.org/10.1161/01.atv.14.2.275. Feb.
[96] Mijatovic V, Kenemans P, Netelenbos JC, Peters-Muller ER, van Kamp GJ, Voetberg GA, van de Weijer PH, van der Mooren MJ. Oral 17 beta-estradiol continuously combined with dydrogesterone lowers serum lipoprotein(a) concentrations in healthy postmenopausal women. J Clin Endocrinol Metab 1997; 82(11):3543–7. https://doi.org/10.1210/jcem.82.11.4357. Nov.
[97] Anagnostis P, Galanis P, Chatzistergiou V, Stevenson JC, Godsland IF, Lambrinoudaki I, Theodorou M, Goulis DG. The effect of hormone replacement therapy and tibolone on lipoprotein(a) concentrations in postmenopausal women: A systematic review and meta-analysis. Maturitas 2017;99:27–36. https://doi.org/10.1016/j.maturitas.2017.02.009. May.
[98] Li C, Wei M, Mo L, Velu P, Prabahar K, Gãman MA, Chen M. The effect of tibolone treatment on apolipoproteins and lipoprotein(a) concentrations in postmenopausal women: A meta-analysis of randomized controlled trials. Eur J Obstet Gynecol Reprod Biol 2024;292:8–16. https://doi.org/10.1016/j.ejogrb.2023.10.020. Jan.
[99] Honigberg MC, Trinder M, Natarajan P. Lipoprotein(a), menopausal hormone therapy, and risk of coronary heart disease in postmenopausal individuals. JAMA Cardiol 2022;7(5):565–8. https://doi.org/10.1001/jamacardio.2022.0716. May 1.
[100] Masson W, Barbagelata L, Corral P, Nogueira JP, Lavalle-Cobo A, Belardo A. Relationship between lipoprotein(a) levels and cardiovascular outcomes in

postmenopausal women: a systematic review. Curr Probl Cardiol 2023;48(4):101589. https://doi.org/10.1016/j.cpcardiol.2023.101589. Apr.

[101] Cook NR, Mora S, Ridker PM. Lipoprotein(a) and cardiovascular risk prediction among women. J Am Coll Cardiol 2018;72(3):287–96. https://doi.org/10.1016/j.jacc.2018.04.060. Jul 17.

[102] Holven KB, Roeters van Lennep J. Sex differences in lipids: a life course approach. Atherosclerosis 2023;384:117270. https://doi.org/10.1016/j.atherosclerosis.2023. Nov.

[103] Elder P, Sharma G, Gulati M, Michos ED. Identification of female-specific risk enhancers throughout the lifespan of women to improve cardiovascular disease prevention. Am J Prev Cardiol 2020;2:100028. https://doi.org/10.1016/j.ajpc.2020.100028. Jun 6.