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Full length article

Maternal and cardiovascular factors related to carotid intima-media thickness during pregnancy: A prospective cohort study

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ABSTRACT

Objective: Cardiovascular disease continues to be the most important cause of death among women worldwide. Carotid intima-media thickness (CIMT) is a well-known indicator of cardiovascular disease. The study aims to establish associations between CIMT measurements and cardiovascular disease risk factors in pregnancy.
Methods: A prospective observational study including normotensive pregnant women. CIMT was measured by mode B-ultrasound in 51 women. Baseline characteristics, weight gain, SBP, DBP, uterine artery Doppler, HbA1c, lipid profile, perceived stress (PSS), anxiety symptoms (STAI) and the level of physical activity during pregnancy were recorded.
Results: Normal reference values (mean ± sd) for CIMT (mm) were described for 20–22 weeks (0.513 ± 0.0067), 28–30 weeks (0.504 ± 0.077) and 33–36 weeks (0.499 ± 0.059). Maternal age was correlated to CIMT (Rho Spearman = 0.392, p = 0.016). However, other variables studied such as weight gain, SBP, DBP, uterine artery Doppler, HbA1c, lipid profile, perceived stress (PSS), and anxiety symptoms (STAI) showed no correlation with CIMT measurements. CIMT was similar in active vs non-active participants (0.540 ± 0.069 vs. 0.489 ± 0.054 mm, p = 0.053). CIMT measurements did not change with gestational age (p = 0.751).
Conclusions: Among normotensive pregnant individuals, CIMT is associated with maternal age but remains stable across gestational age and unaffected by various cardiovascular risk factors during pregnancy.

Introduction

Cardiovascular disease (CVD) remains the most important cause of death among women worldwide [1]. Carotid intima media thickness (CIMT) is a non-invasive, sensitive, and reproducible marker of atherosclerotic disease predictive of risk of subsequent cardiovascular events [2]. During pregnancy, changes in blood volume and metabolic requirements contribute to hemodynamic and vascular adaptations [3]. In addition, adverse perinatal outcomes are linked to an increased risk of CVD later in life [4].

In women with elevated CIMT during pregnancy, the negative effect of pregnancy on CIMT may persist for more than two years after childbirth, making it a potential long-term risk factor [5]. CIMT has been found to be increased in women with preeclampsia compared to normotensive pregnant women and therefore, may have a role in antenatal care to identify women at high risk of pre-eclampsia [6,7] and increase risk of CVD later in life [6,7]. There is growing interest in using markers of subclinical atherosclerosis during pregnancy to predict women at risk of developing pre-eclampsia [6,8]. Postpartum CIMT may help recognizing women at high cardiovascular risk following pre-eclampsia enabling the implementation of lifestyle interventions and appropriate surveillance [9]. Furthermore, CIMT appeared to be higher in women with history of pregnancy loss [10].

Few studies have examined CIMT during pregnancy and its

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association with maternal factors. Increased CIMT has been associated with maternal age and Body Mass Index (BMI) [11]. Regarding parity, results are conflicting [11,12]. Other factors such as physical activity or mental health during pregnancy may affect the CIMT, and therefore the CVD risk in women. Exercise is associated with reduced CIMT in general population [13], while anxiety and depressive symptoms are linked to increase CIMT in the general population without heart disease or stroke [14]. However, these factors have not been thoroughly evaluated during pregnancy Nevertheless, there is still much to be learned about how maternal factors and pregnancy-related changes may affect CVD risk, and the role of CIMT needs to be clearly defined during pregnancy.

This study aims to establish is if there are associations between CIMT measurements and CVD risk factors in pregnancy.

Methods

Study design

This is a prospective observational study including normotensive pregnant from Hospital Vall d'Hebrón, Barcelona, Spain. These women were followed-up in the ACPREGCOV (Active Pregnancy against COVID-19, NCT: NCT04563065) study, a randomized controlled trial evaluating the impact of a moderate exercise program throughout the pregnancy, on maternal, fetal, and neonatal health.

Participants

Participants were prospectively recruited if they met the inclusion criteria: singleton pregnancy, above 18 years old, planning delivery at the research hospital, and not participating in any other program of exercise. Exclusion criteria included the absolute contraindications for the practice of exercise during pregnancy [15,16]. Women were included in the study before 17 weeks of pregnancy, and were randomized to a physical activity program vs. control group.

Variables

Dependent variable was the CIMT measured by mode B-ultrasound. Independent variables included were maternal age, weight, BMI before pregnancy and at recruitment, type of conception, parity, ethnicity, previous miscarriages, pregnancy risk, self-reported level of physical activity before pregnancy, smoker before pregnancy. During the pregnancy, the following variables were included: Systolic Blood pressure (SBP), diastolic blood pressure (DBP), uterine artery Doppler, HbA1c, lipid profile, perceived stress, and anxiety symptoms and the level of physical activity during pregnancy.

Pregnancy risk was based on the local antenatal care protocol, including those with medium, high and very high risk [17]. Pregnant women who present any of the risk factors that make up this group and that may increase the likelihood of complications appearing during the gestation period or during childbirth will be classified in the pregnancy risk group, thus increasing perinatal morbidity and mortality. All participants included were normotensive, defined as systolic blood pressure (SBP) < 140 mmHg and diastolic blood pressure (DBP) < 90 mmHg before 20 weeks of gestation, without a previous diagnosis of chronic hypertension. Additionally, none of the participants developed hypertensive disorders during pregnancy.

Data source/measurements

Carotid ultrasonography. All measurements were obtained using the Samsung Hera W10 ultrasound system and the probe LA2-14A (SamsungTM Medison, Seoul, South Korea). The ultrasound system was used in accordance with training provided by the manufacturer. The sonographers (AF, TH, IC and MB), certified by the FMF for obstetric ultrasound, had a uniform training provided by a senior practitioner researcher CIMT expert before recruitment began. CIMT values were obtained using a fully automated technique. A cine-loop was automatically analysed, and the automated technique measured CIMT at a predefined point at which the measurement was more reproducible. The automated software determined the intima-media boundary of a segment of the far wall of the common carotid. The mean CIMT values were calculated from the segment selected and the mean CIMT was recorded in the right and left common carotid arteries. If the intima-media layer of the distal wall was incorrectly identified, the selected boundaries of the intima-media layer were edited and corrected; therefore, we use a semiautomatic CIMT software. High-resolution B-mode compression ultrasound was performed using a linear array transducer (nominal bandwidth of 5–10 MHz) with 8 MHz centre frequency. The frame rate was 29fps for the image acquisition. For the analysis, at least 1 cm below the origin of the carotid bulb of the common carotid artery (CCA) was used. Two measurements for the right and left carotid arteries were obtained, and we calculated and recorded the mean of the right and left common carotid arteries [18]. CIMT was measured at 20-22w, 28-30w and 33-36w.

Maternal weight was assessed at first (11-13w), second (20-22w), and third (33-36w) trimesters. Participants were weighed on a digital scale in kilograms while barefoot.

Physical activity level before pregnancy was assessed as a self-reported variable (inactive, active, very active, elite athlete) during the first trimester. During pregnancy, physical activity was categorized as 'active' for those in the exercise group who complied with more than 80 % of the physical activity program (50-minute moderate-intensity classes, three times per week) and 'inactive' for those with less than 80 % compliance, and the participants in the control group.

SBP, DBP and calculated MBP were recorded for study purposes at first (11-13w) and third (33-36w) trimesters. They were assessed using an Omron M6 Comfort, in a sitting position, in the right arm, following the ACC/AHA Hypertension guidelines [19].

Right and Left uterine artery Doppler Pulsatiliy Index (Ut A PI) were measured at 34-36w and mean Ut A PI calculated. A Voluson GE e10 (GE Healthcare, Zipf, Austria) ultrasound machine with a convex transducer (RAB6-RS) was used.

Blood analyses included HbA1c in the second trimester (24-26w), and lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, Triglycerides at 34-36w.

The Perceived Stress Scale 10 (PSS-10) questionnaire was used to assess stress, and the State-Trait Anxiety Inventory (STAI) was used to assess anxiety. The PSS-10 is a 10-item questionnaire [20], widely used to assess stress levels in both young people and adults [23]. The STAI is the primary rating scale for measuring state (STAI-S) and trait (STAI-T) anxiety [21]. It consists of 40 self-administered items rated on a 4-point scale ranging from 0 to 3. The STAI has been validated for use in pregnant women [22]. Both the PSS and STAI were assessed at baseline and at 34–36 weeks of pregnancy.

Statistical analysis

Data analysis was carried out using "R" software (R version 4.2.2), Copyright (C) 2015 The R Foundation for Statistical Computing. Normally distributed data were displayed as means and standard deviations (SDs), while non-normally distributed data were displayed as medians and interquartile ranges (IQRs). Spearman's bivariate correlation was used to determine the relationships between semi-automated CIMT measurements and baseline maternal demographic and other pregnancy measured factors. A Mann-Whitney *U* test was performed to assess the difference between semi-automated CIMT measurements of qualitative variables. If more than 2 categories, ANOVA or Kruskal Wallis were used. A p value below 0.05 was regarded as statistically significant.

Statistical analysis has been carried out by the Statistics and Bioinformatics Unit (UEB) Vall d'Hebrón Hospital Research Institute (VHIR).

Ethics

Ethical approval for this study was received from the Ethics Committee of the Vall d'Hebrón Institute of Research, Barcelona (PR(AMI) 504/2019). All participating women signed the consent for prior recruitment.

Results

Participants

From 57 women that agreed to participate in the ACPREGCOV study at Hospital Vall d'Hebrón, 6 cases were lost since CIMT automatic software unavailability. In the final cohort, 51 participants had at least one measurement of CIMT and were included for the study purposes.

Descriptive data

Maternal baseline characteristics and pregnancy variables were thoroughly analyzed to provide a comprehensive overview of the study population (Table 1). Mean maternal age was 35.4 ± 5.7 years old and BMI before pregnancy 26.3 ± 7.2. Thirty-five out of 51 (68.6 %) were nulliparous and 28 out of 51(54.9 %) presented a pregnancy risk.

Carotid intima-media thickness (CIMT) measurements were obtained longitudinally across three gestational age ranges: 20–22 weeks, 28–30 weeks, and 34–36 weeks. Table 2 shows the reference values of the mean of CIMT of 0.513, 0.504, and 0.499 mm in these time frames respectively. The study included 28 high-risk pregnancies with the following diagnosis: haematological diseases (Von Willebrand, thrombophilia), mental health disorders, epilepsy, asthma, hypothyroidism, multiple sclerosis, type 1 diabetes and obesity (BMI > 30).

Table 1
Maternal baseline characteristics (N = 51).

Maternal baseline variables	Mean (SD)	95 % CI median [IQR]
Maternal age (years)	35.4(5.7)	[33.8; 37.0] 36 [31,39]
BMI before pregnancy	26.3(7.2)	[24.3;28.4] 24.4[21.5,30.6]
BMI at recruitment	27.0(7.1)	[25;29.1] 25.2 [22.1,30.6]
Anxiety symptoms (STAI) 1st trimester (n = 50)	46.3 (25.3)	[39.1;53.4] 41.5 [28,62.5]
Stress symptoms (PSS) 1st trimester	20 (2.9)	[19.2;20.8] 20 [18.2,21.8]
	N (%)	**95 %CI**
Nulliparous	35(68.6)	[54.1; 80.9]
University educational level	30(58.8)	[44.2; 72.4]
Assisted reproductive technique	14(27.5)	[15.9; 41.7]
Pregnancy Risk*	28(54.9)	[42.2; 71.2]
Self-reported level of physical activity prior pregnancy		
Inactive	9 (18.8)	[8.9; 32.6]
Sedentary	23 (47.9)	[33.3; 62.8]
Active	12 (25)	[13.6; 39.6]
Very active	4 (8.3)	[2.3; 20]
Smoker before pregnancy	9 (17.6)	[8.4; 30.9]
Caucasian	40 (80)	[66.3; 90]
Previous miscarriages	22 (43.1)	[29.3; 57.8]

N (%): Number of participants (percentage), 95% CI: 95% confidence interval. Mean (SD): Mean (Standard Deviation), 95% CI: 95% confidence interval, Median [IQR]: Median [Interquartile Range].
*Pregnancy Risk with antenatal care by obstetric consultant according to the local protocol.

Table 2
CIMT measurements across the pregnancy.

Gestational Age	N	Mean	SD	IQR
20-22w	37	0.513	0.067	0.477–0.555
28-30w	36	0.504	0.077	0.455–0.567
34-36w	36	0.499	0.059	0.455–0.550

N: Number of participants, SD: Standard Deviation, IQR: Interquartile Range.

Factors related to basal CIMT (20-22w)

Baseline characteristics were studied related to CIMT baseline measurement at 20-22w. Gestational age at measurement was 19.6 ± 0.5 weeks. Maternal age was the only factor that was correlated to CIMT (Rho Spearman = 0.392, p = 0.016) (Fig. 1). However, no correlation was found with BMI before pregnancy (Rho = 0.144, p = 0.395), or at first trimester (Rho = 0.145, p = 0.392), nor anxiety symptoms (Rho = -0.148, p = 0.389) or perceived stress (Rho = -0.231, p = 0.175). When evaluating level of physical activity before pregnancy (p = 0.927) or parity (p = 0.143) or smoker before pregnancy (p = 0.368), none of them were associated with CIMT measurement at 20–22 weeks.

Factors related to CIMT (33-36w)

Pregnancy cardiovascular risk variables, mental health and exercise variables were studied as related to CIMT at 33-36w. Gestational age at measurement was 34.8 ± 0.7 weeks. A correlation analysis was performed including variables such as SPB (Rho = -0.054, p = 0.754), DBP (Rho = -0.280, p = 0.99), Mean Ut A PI (Rho = -0.276, p = 0.107), Total Cholesterol (Rho = -0.035, p = 0.857), STAI (Rho = -0.283, p = 0.145), PSS (Rho = -0.234, p = 0.169), measured at 33-36w, and HbA1c measured at 24-28w (Rho = 0.057, p = 0.744) (Fig. 2). In regards to maternal weight gain during pregnancy, it was not related to CIMT (Rho = -0.123, p = 0.651). When analysing those women who had been active vs. non-active during pregnancy, no differences were found in the CIMT (0.540 ± 0.069 vs. 0.489 ± 0.054, Rho = 0.325, p = 0.053).

Changes of CIMT measurements during pregnancy

Eighteen participants had all three CIMT measurements during pregnancy, and the changes thought-out the pregnancy were assessed. Fig. 3 shows that CIMT measurements did not change with gestational age (p = 0.751).

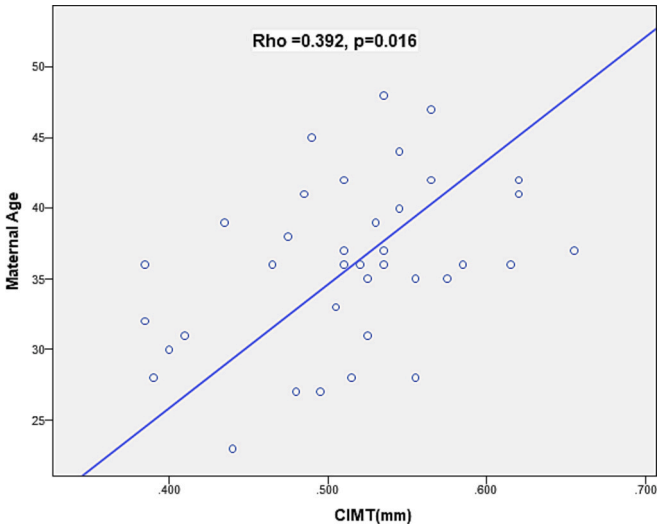

Fig. 1. Correlation between Maternal Age and CIMT at 20-22w.

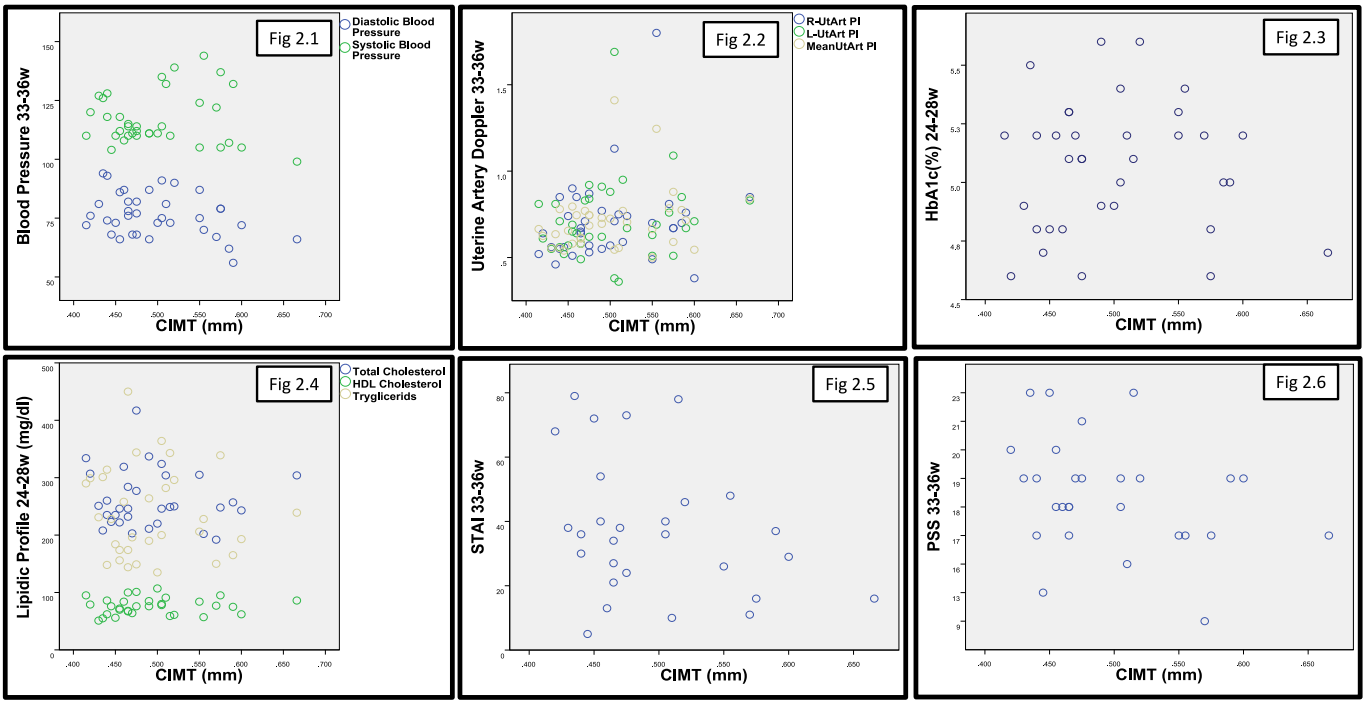

Figure 2. Correlation between cardiovascular factors, uterine arteries blood flow, perceived stress (PSS) and anxiety symptoms (STAI), and CIMT at 33-36w.
Fig2.1: Blood Pressure. Figure 2.2: Uterine Artery Doppler, Figure 2.3: HbA1c(%), Figure 2.4: Blood Lipid profile including: Total Cholesterol, HDL Cholesterol, LDL Cholesterol and Triglycerides. Figure 2.5: STAI measuring anxiety, Figure 2.6: PSS, measuring perceived stress

Fig. 2. Correlation between cardiovascular factors, uterine arteries blood flow, perceived stress (PSS) and anxiety symptoms (STAI) and CIMT at 33-36w.

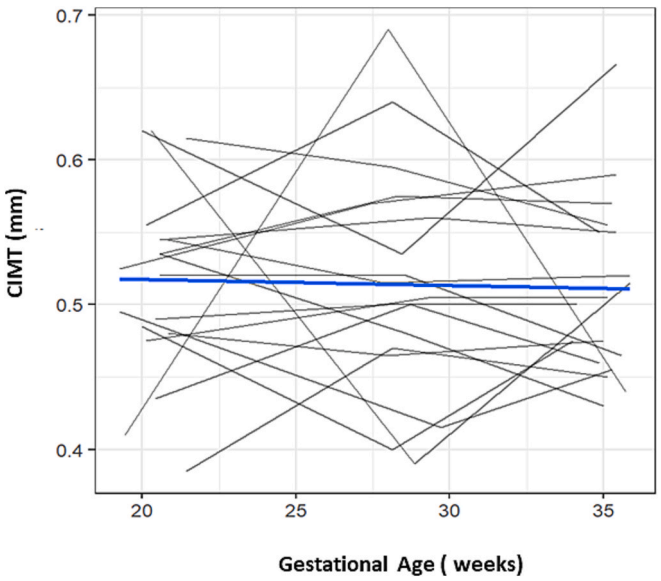

Fig. 3. Evolution of CIMT according to gestational age (weeks).

Discussion

Main results

Pregnancy induces significant physiological changes in the maternal cardiovascular system, which can influence measurements of CIMT [23]. This study aimed to establish is if there were associations between CIMT measurements and CVD risk factors in pregnancy. Our findings include, first, CIMT measured at 20–22 weeks is positively associated with maternal age in normotensive pregnancies. Second, CIMT measurements are independent of gestational age. Third, mental health, physical activity, and other cardiovascular risk factors do not appear to influence CIMT measurements during pregnancy. To our knowledge, this is the first study to incorporate variables such as physical activity, mental health and cardiovascular factor variables to examine their relationship with CIMT measurements.

Our results suggest that CIMT measurements during pregnancy may be comparable to those in non-pregnant individuals, as CIMT appears to be largely unaffected by the physiological changes that occur during pregnancy. However, since data from the first trimester CIMT was not available for analysis, changes in CIMT between the first and second trimesters cannot be entirely excluded in this study.

Comparison with previous studies

CIMT is associated with CVD risk factors, prevalent CVD, incident CVD, and the degree of atherosclerosis in several different arterial sites [24,25]. As such, it has been used as a surrogate marker of atherosclerosis [18]. Increased CIMT may result from intimal or medial hypertrophy or both, and may be an adaptive response to changes in flow, wall tension, or lumen diameter [26].

Our result show that CIMT measurements during pregnancy are associated with maternal age. This finding aligns with the literature reporting that CIMT is linearly and strongly related to age, independent of other CVD or risk factors [27]. An association between CIMT and maternal age during pregnancy has been previously documented [11].

However, parity does not associate with CIMT during pregnancy according to our results. Nevertheless, there are inconsistent results in the literature between CIMT and parity [11,28].

Similarly, other cardiometabolic factors such as BMI, maternal weight gain, lipid profile or blood pressure are not associated with CIMT measured during pregnancy. Despite the known association between increased BMI and risk of CVD [29], it is not clear that BMI is associated with CIMT. No association was observed with blood pressure either,

which may be due to our study's focus on normotensive pregnant women. Regarding lipid profile, most of the studies have focused on non-pregnant populations [30,31] making difficult to draw direct comparisons, as lipids concentrations physiologically change during pregnancy.

There is substantial evidence showing that unhealthy lifestyles negatively affect long-term cardiovascular health [32]. Therefore, in the present study, we have included anxiety, perceived stress and physical activity during pregnancy, but found no association with CIMT. We believe that nine months is a too short period to be able to reflect changes in the CIMT due to deleterious lifestyles. Otherwise, these changes have already been demonstrated in non-pregnant population longitudinal studies [13,14]. Our findings suggest that CIMT during pregnancy is independent of anxiety, stress, or physical activity levels.

We established normal reference values of CIMT measurements in normotensive pregnant population, across three trimesters of pregnancy, being similar to that reported in non-pregnant population [33,34]. For CIMT measurement, we used the semi-automatic ultrasound technique, which is widely recommended for its accuracy and reliability [18,33].

Normal reference values for carotid intima-media thickness (CIMT) in the non-pregnant population have been widely established in previous studies, showing significant variations based on factors such as age and gender. CIMT values in a healthy adult population vary with age, with an average thickness of around 0.5 mm in young individuals, gradually increasing with age, particularly in those over 60 years, where values can exceed 1.0 mm [35]. There is also gender disparities in the CIMT measurement, highlighting that men tend to have a slightly higher CIMT than women [36,37]. These data emphasize the importance of considering CIMT as a cardiovascular risk assessment tool, with values dependent on the demographic characteristics of the population.

Most of the studies include CIMT measurements during postpartum or long term and there is ample evidence supporting that women affected by preeclampsia during pregnancy have higher CIMT measurements after pregnancy, increasing therefore their cardiovascular risk [38]. It has been suggested to include the CIMT during pregnancy as a marker to predict preeclampsia (PE) since PE participants showed higher CIMT measurements during pregnancy compared to normotensive pregnant population [6]. Nevertheless, women who had PE had significantly higher CIMT compared to those without PE, both at the time of diagnosis and in the first decade, suggesting that atherosclerotic load is present at the time of PE [39].

Strengths and limitations

The strengths of this study include its thorough examination of mental health, physical activity, and cardiovascular factors during pregnancy, as well as the use of longitudinal CIMT measurements and the establishment of normal reference values for CIMT in normotensive pregnant individuals. In addition, the study benefited from highly experienced sonographers who received specific training for CIMT measurement and the inclusion of a representative normotensive pregnant population. However, the study is constrained by its sample size, the lack of a non-pregnant population comparison as a control, and the absence of CIMT measurements in the first trimester, which limits the assessment of early gestational changes and hinders direct comparisons with non-pregnant individuals. Furthermore, the study's focus on normotensive pregnant individuals means that its findings cannot be generalized to hypertensive populations, which warrants caution when interpreting the results for individuals with pregnancy-induced hypertension.

Due to the reduced number of participants, it was not possible to perform a regression analysis to state that maternal age was an independent predictor of CIMT during pregnancy. In addition, the inclusion of participants with type 1 diabetes or obesity, could represent a selection bias, since both increase long term cardiovascular risk. This fact could restrict the generalizability of the study results. Furthermore, this study did not evaluate the association between inflammatory biomarkers (such as neutrophil-to-lymphocyte ratio [NLR] and red cell distribution width [RDW]) and CIMT in normotensive pregnant women. Inflammation is known to play a significant role in vascular remodeling and endothelial function during pregnancy. Recent studies have highlighted a strong relationship between elevated inflammatory markers and increased CIMT in healthy individuals [40,41]. The absence of these data limits our ability to explore the potential contribution of systemic inflammation to vascular changes during pregnancy, which could be an important area for future research. Additionally, this study did not include hypertensive pregnant individuals, so its conclusions cannot be extrapolated to this population.

Conclusion

Among normotensive pregnant individuals, CIMT during pregnancy is associated with maternal age, remains consistent throughout gestation, and is not influenced by other cardiovascular risk factors. Further research is needed to validate these results and assess their applicability to other populations, such as those with hypertension during pregnancy.

CRediT authorship contribution statement

Maia Brik: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Miguel Sánchez-Polán:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Conceptualization. **Alba Farràs:** Writing – review & editing, Software, Resources, Methodology, Investigation, Conceptualization. **Alina Hernández-Fleury:** Writing – review & editing, Software, Project administration, Methodology, Data curation. **Joaquin Temprado:** Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Inés Calero:** Writing – review & editing, Software, Resources, Methodology, Investigation. **Teresa Higueras:** Writing – review & editing, Software, Resources, Methodology, Investigation, Conceptualization. **Cristina Silva:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Dingfeng Zhang:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Elena Carreras:** Writing – review & editing, Visualization, Supervision, Resources, Funding acquisition, Conceptualization. **Ruben Barakat:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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