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Association of Reproductive Factors with Cardiovascular Risk Markers in Women: A Hospital-Based Study

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ABSTRACT
Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among women worldwide, with emerging evidence suggesting that reproductive factors significantly influence long-term cardiometabolic risk. This hospital-based cross-sectional study aimed to evaluate the association between reproductive characteristics and cardiovascular risk markers among women attending a tertiary care center. A total of 312 women aged 25–65 years were enrolled between January 2022 and December 2023. Detailed reproductive histories, including age at menarche, parity, age at first pregnancy, menopausal status, history of gestational diabetes, hypertensive disorders of pregnancy, and oral contraceptive use, were recorded. Cardiovascular risk markers assessed included body mass index (BMI), waist-to-hip ratio (WHR), fasting lipid profile, fasting plasma glucose (FPG), and high-sensitivity C-reactive protein (hs-CRP). Early menarche (<12 years) was significantly associated with higher BMI (29.4 ± 4.1 kg/m² vs 26.8 ± 3.7 kg/m², $p < 0.001$) and elevated triglycerides ($p = 0.002$). Multiparity (≥3 births) correlated with increased WHR (0.91 ± 0.05 vs 0.86 ± 0.04, $p < 0.001$) and higher FPG ($p = 0.01$). Postmenopausal women demonstrated significantly elevated LDL cholesterol and hs-CRP levels ($p < 0.001$). History of gestational diabetes independently predicted metabolic syndrome (OR 2.8; 95% CI 1.4–5.6; $p = 0.003$). Reproductive factors are significantly associated with adverse cardiovascular risk markers, emphasizing the importance of incorporating reproductive history into cardiovascular risk stratification in women.

Keywords: Reproductive health; Cardiovascular risk; Menopause; Parity; Metabolic syndrome

INTRODUCTION

Cardiovascular disease (CVD) is widely recognized as the leading cause of death among women globally, surpassing mortality from malignancies and infectious diseases. According to global health estimates, nearly one in three female deaths is attributable to cardiovascular causes, including ischemic heart disease, stroke, and heart failure [1]. Historically, CVD was perceived as predominantly affecting men; however, contemporary research has clarified that women experience unique pathophysiological mechanisms, clinical presentations, and risk profiles. Notably, traditional risk factors such as hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking do not fully account for the variation in cardiovascular risk observed among women [2]. Increasing attention has therefore been directed toward female-specific determinants, particularly reproductive factors, which may influence long-term cardiometabolic health.

Reproductive life events represent complex physiological transitions involving substantial hormonal fluctuations. Age at menarche marks the onset of endogenous estrogen exposure, while menopause signifies its decline. Estrogen has protective effects on vascular endothelium, lipid metabolism, and inflammatory pathways; thus, variations in duration of reproductive years may influence cumulative cardiovascular risk [3]. Early menarche has been linked to obesity, insulin resistance, and metabolic syndrome in adulthood [4]. Conversely, late menopause has been associated with prolonged estrogen exposure, which may confer protective vascular effects but also

increases risk for certain malignancies [5]. Despite these associations, population-specific evidence remains inconsistent, particularly in South Asian settings.

Parity and pregnancy-related complications further contribute to cardiovascular risk. Pregnancy induces profound hemodynamic and metabolic changes, including increased cardiac output, insulin resistance, and lipid alterations. While these changes are typically reversible postpartum, women with multiple pregnancies or complicated gestations may experience persistent vascular dysfunction [6]. Hypertensive disorders of pregnancy, including preeclampsia, have been associated with increased risk of chronic hypertension and ischemic heart disease later in life [7]. Similarly, gestational diabetes mellitus (GDM) significantly elevates the future risk of type 2 diabetes and metabolic syndrome [8]. These findings underscore pregnancy as a "stress test" for the cardiovascular system.

Menopause represents another critical transition associated with acceleration of atherosclerotic processes. The decline in estrogen levels contributes to adverse lipid profile changes, endothelial dysfunction, increased visceral adiposity, and systemic inflammation [9]. Postmenopausal women exhibit higher low-density lipoprotein (LDL) cholesterol, reduced high-density lipoprotein (HDL) cholesterol, and elevated inflammatory markers compared with premenopausal women [10]. The timing and duration of menopause may therefore modify cardiovascular risk trajectories. However, data from hospital-based South Asian populations are limited, and cultural factors influencing reproductive patterns warrant investigation.

Oral contraceptive use and hormonal therapies have also been evaluated for cardiovascular implications. Combined estrogen-progestin formulations may increase risk of thromboembolic events, particularly in women with pre-existing risk factors [11]. Conversely, some studies suggest neutral or beneficial effects on lipid metabolism when used appropriately [12]. Variability in formulations, duration of use, and patient characteristics complicates interpretation of existing evidence.

In Pakistan and similar low- and middle-income countries, women often experience early marriages, high parity, and limited access to preventive healthcare services [13]. These sociocultural factors may amplify cardiometabolic risk. Yet, few hospital-based studies systematically evaluate the combined impact of reproductive factors on objective cardiovascular risk markers such as lipid profile, fasting glucose, and inflammatory biomarkers. Most available research is community-based and lacks detailed biochemical assessment [14]. Therefore, context-specific evidence is essential to guide clinical practice and public health interventions.

The present study was designed to evaluate the association between key reproductive factors—including age at menarche, parity, menopausal status, gestational diabetes, hypertensive disorders of pregnancy, and oral contraceptive use—and established cardiovascular risk markers among women attending a tertiary care hospital. By integrating reproductive history into cardiometabolic profiling, this study aims to provide evidence for personalized cardiovascular risk assessment strategies tailored to women in hospital settings [15].

MATERIALS AND METHODS

Study Design and Setting

This hospital-based cross-sectional analytical study was conducted at Jinnah Hospital, Pakistan. Ethical approval was obtained from the Institutional Review Board (Reference No: LGH-IRB/2021/Med-074). The study adhered to the Declaration of Helsinki.

Sample

A total of 312 women aged 25–65 years attending outpatient medical clinics were enrolled through consecutive sampling. Sample size was calculated using a 95% confidence level, 5% margin of error, and expected 30% prevalence of metabolic syndrome, yielding a minimum required sample of 280; 312 were included to enhance statistical power.

Inclusion/ Exclusion criteria

Inclusion criteria were women aged 25–65 years with at least one prior pregnancy and complete reproductive history documentation.

Exclusion criteria included known cardiovascular disease, chronic kidney disease, active malignancy, current pregnancy, hormone replacement therapy, and inflammatory or autoimmune disorders.

Data Collection

Structured interviews recorded sociodemographic characteristics and reproductive history:

- Age at menarche
- Parity
- Age at first pregnancy
- Menopausal status
- History of gestational diabetes
- History of hypertensive disorders of pregnancy
- Duration of oral contraceptive use

Anthropometric measurements included BMI and waist-to-hip ratio (WHR). Blood pressure was recorded using a calibrated sphygmomanometer.

Laboratory Investigations

After overnight fasting, blood samples were analyzed for:

- Fasting plasma glucose (FPG)
- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides
- High-sensitivity C-reactive protein (hs-CRP)

Metabolic syndrome was defined according to

International Diabetes Federation criteria.

Statistical analysis

Data were analyzed using SPSS version 26. Continuous variables were expressed as mean ± SD. Independent t-test and ANOVA compared group means. Chi-square test assessed categorical variables. Multivariate logistic regression evaluated predictors of metabolic syndrome. $p < 0.05$ was considered statistically significant.

RESULTS

Table 1. Baseline Characteristics

Variable	Mean ± SD / n (%)
Age (years)	42.3 ± 9.6
Early menarche (<12 yrs)	68 (21.8%)
Multiparity (≥3 births)	124 (39.7%)
Postmenopausal	118 (37.8%)
History of GDM	46 (14.7%)
History of HDP	39 (12.5%)

Table 2. Association of Reproductive Factors with Cardiovascular Risk Markers

Variable	BMI	LDL	Triglycerides	hs-CRP
Early menarche	29.4 ± 4.1	138 ± 28	186 ± 34	4.1 ± 1.2
Normal menarche	26.8 ± 3.7	124 ± 25	158 ± 29	3.2 ± 1.0
p-value	<0.001	0.01	0.002	0.01

Table 3. Predictors of Metabolic Syndrome

Factor	OR	95% CI	p-value
Multiparity	2.1	1.3–3.5	0.004
GDM history	2.8	1.4–5.6	0.003
Postmenopause	1.9	1.1–3.2	0.02

Women with early menarche demonstrated significantly higher BMI, triglycerides, LDL cholesterol, and hs-CRP compared with those with normal menarche. Multiparity and postmenopausal status were associated with adverse lipid profiles and central obesity. History of gestational diabetes emerged as the strongest independent predictor of metabolic syndrome.

DISCUSSION

This study demonstrates significant associations between reproductive factors and cardiovascular risk markers among hospital-attending women. Early menarche was linked to higher BMI and dyslipidemia, supporting hypotheses that prolonged estrogen exposure combined with early adiposity contributes to metabolic risk. Multiparity showed strong correlation with central obesity and metabolic syndrome, potentially reflecting cumulative metabolic stress from repeated pregnancies.

Postmenopausal women exhibited higher LDL cholesterol and inflammatory markers, consistent with estrogen deficiency–mediated vascular changes. History of gestational diabetes independently predicted metabolic syndrome, reinforcing the concept of pregnancy as an early indicator of future cardiometabolic vulnerability.

The findings underscore the importance of integrating reproductive history into cardiovascular risk assessment frameworks, particularly in South Asian populations with high parity and early reproductive age patterns.The present hospital-based study demonstrates a significant association between reproductive factors and objective cardiovascular risk markers among women, reinforcing the concept that reproductive history is an integral component of long-term cardiometabolic risk stratification. Our findings indicate that early menarche, multiparity, postmenopausal status, and history of gestational diabetes mellitus (GDM) are independently associated with adverse metabolic profiles, including elevated body mass index (BMI), central obesity, dyslipidemia, systemic inflammation, and metabolic syndrome. These observations align with the growing body of literature suggesting that female-specific life events exert sustained physiological effects extending beyond the reproductive years [16].

Early menarche was significantly associated with higher BMI, elevated triglycerides, increased LDL cholesterol, and raised hs-CRP levels. This finding supports epidemiological evidence indicating that early onset of menarche correlates with childhood adiposity and subsequent adult metabolic dysfunction [17]. Earlier exposure to endogenous estrogen may influence adipocyte differentiation and fat distribution, particularly promoting central adiposity, which is metabolically active and pro-inflammatory [18]. Inflammatory markers such as hs-CRP, observed to be elevated in this subgroup, are recognized predictors of atherosclerotic cardiovascular disease. Previous cohort studies have similarly demonstrated that women experiencing menarche before 12 years of age have a significantly increased risk of coronary heart disease and stroke later in life [19]. Our results confirm these associations within a hospital-based South Asian population, where early puberty may be influenced by nutritional and environmental transitions.

Multiparity emerged as another significant determinant of cardiometabolic risk. Women with three or more births had higher waist-to-hip ratios and fasting plasma glucose levels and were more likely to meet criteria for metabolic

syndrome. Pregnancy induces a state of physiological insulin resistance, hyperlipidemia, and increased oxidative stress. While these adaptations support fetal development, repeated pregnancies may lead to incomplete metabolic recovery postpartum [20]. Several longitudinal studies have reported a dose-response relationship between number of pregnancies and later-life cardiovascular disease risk [21]. Moreover, multiparity has been associated with increased visceral adiposity, independent of age and lifestyle factors [22]. Our findings are consistent with these observations and suggest that repeated gestational metabolic stress contributes to persistent metabolic remodeling.

Postmenopausal status was significantly associated with elevated LDL cholesterol and higher hs-CRP levels. The decline in estrogen during menopause results in reduced hepatic LDL receptor activity, increased LDL particle concentration, and impaired endothelial function [23]. Estrogen deficiency also promotes redistribution of fat from peripheral to central compartments, thereby exacerbating insulin resistance and systemic inflammation [24]. In our study, postmenopausal women had nearly double the odds of metabolic syndrome compared with premenopausal participants. These results parallel prior investigations demonstrating accelerated atherosclerotic progression after menopause [25]. Importantly, the association persisted after adjustment for age, underscoring the independent contribution of hormonal transition rather than chronological aging alone.

A history of gestational diabetes mellitus (GDM) emerged as the strongest independent predictor of metabolic syndrome in our cohort. Women with prior GDM had nearly threefold increased odds of developing metabolic syndrome. GDM reflects underlying beta-cell dysfunction and insulin resistance, which may persist or progress postpartum [26]. Meta-analyses have demonstrated that women with prior GDM have a markedly increased risk of type 2 diabetes and cardiovascular disease within 10–20 years after pregnancy [27]. Inflammatory and endothelial dysfunction pathways activated during hyperglycemia may initiate long-term vascular injury [28]. Our findings highlight the importance of structured postpartum follow-up and early cardiometabolic screening among women with a history of GDM, particularly in resource-limited healthcare systems where follow-up may be inconsistent.

Hypertensive disorders of pregnancy (HDP), although less prevalent in our sample, also demonstrated a trend toward higher blood pressure and lipid abnormalities. HDP is recognized as an early marker of endothelial dysfunction and future cardiovascular disease risk [29]. The pathophysiological overlap between preeclampsia and atherosclerosis includes oxidative stress, inflammation, and impaired nitric oxide signaling. Although our study did not demonstrate statistical significance after multivariable adjustment, likely due to sample size limitations, the observed pattern supports existing evidence advocating long-term surveillance in this high-risk subgroup [30].

The clinical implications of these findings are substantial. Traditional cardiovascular risk assessment models often exclude reproductive history, potentially underestimating risk in women. Incorporating reproductive milestones such as age at menarche, parity, menopausal status, and pregnancy complications into routine clinical evaluation could improve early identification of high-risk individuals. In South Asian populations, where high parity and early reproductive age are common, such integration may be particularly impactful. Additionally, hospital-based screening programs can leverage obstetric and gynecological visits as opportunities for cardiovascular risk counseling.

Strengths of this study include detailed biochemical assessment, standardized measurement of inflammatory markers, and multivariate adjustment for confounders. However, certain limitations warrant consideration. The cross-sectional design precludes causal inference, and longitudinal follow-up would better establish temporal relationships. Recall bias may have influenced self-reported reproductive history. Furthermore, as the study was conducted in a single tertiary hospital, findings may not fully generalize to rural or community populations.

Despite these limitations, the study contributes valuable region-specific data supporting the association between reproductive factors and cardiovascular risk markers. It underscores the concept that reproductive life events serve as early biological indicators of future cardiometabolic vulnerability. Future prospective cohort studies should explore mechanistic pathways linking hormonal transitions to vascular dysfunction and evaluate targeted prevention strategies tailored to reproductive risk profiles.

In summary, the discussion affirms that early menarche, multiparity, menopause, and gestational diabetes are significantly associated with adverse cardiovascular risk markers in women. Recognition of these associations provides an opportunity to shift cardiovascular prevention strategies toward a life-course approach that integrates reproductive health with cardiology practice.

CONCLUSION

Reproductive factors—including early menarche, multiparity, postmenopausal status, and gestational diabetes—are significantly associated with adverse cardiovascular risk markers in women. Incorporating reproductive history into routine cardiovascular screening may enhance early identification of high-risk individuals and improve preventive strategies.

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ETHICS STATEMENT

Approved by LGH-IRB/2021/Med-074.

INFORMED CONSENT

Written informed consent was obtained from all participants.

COMPETING INTERESTS

None declared.

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