International Journal of Medical Science and Clinical Invention 11(10): 7274-7287, 2024
DOI:10.18535/ijmsci/v11i.10.02
https://valleyinternational.net/index.php/ijmsci

Pregnancy Complications and Development of Chronic Disease in Later Life

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Abstract
The majority of pregnancy-related health issues seem to go away at delivery or very soon after. Preterm labour, placental abruption, preeclampsia, and gestational diabetes are common examples. It is well established that women who experience these kinds of issues throughout their pregnancies are more likely to experience similar issues in subsequent pregnancies. Pregnancy puts a strain on a woman's body, it can reveal underlying predispositions to disease that would otherwise go undetected for years, and this association between various pregnancy complications and the development of chronic disease in later life has gained recognition. However, despite the growing body of data, healthcare providers are not aware of these risks.

Keywords: Maternity, Post-pregnancy, long term effects, preeclampsia, gestational diabetes

Introduction

A woman's physiological function is significantly altered during pregnancy in order to assist the developing foetus. [1] Because of the strain placed on the body of the expectant mother, it is known as nature's "stress test" and may indicate a chronic illness propensity years earlier than it otherwise would have. [1,2] Pregnancy difficulties are known to have a deleterious impact on both mother and child outcomes, and there is mounting evidence that they are linked to maternal health issues long after the pregnancy has ended. For instance, the risk of developing type 2 diabetes (T2DM) is well-established in relation to gestational diabetes (GDM); however, women's healthcare professionals are far less aware of other long-term health hazards that may arise from issues during pregnancy. [3,4] The majority of pregnancy-related health issues seem to go away at delivery or very soon after. Preterm labour, placental abruption, preeclampsia, and gestational diabetes are common examples. It is well established that women who experience these kinds of issues throughout their pregnancies are more likely to experience similar issues in subsequent pregnancies. Premature mothers are more likely to experience recurrent preterm labour; women who developed gestational diabetes (GDM) are more likely to develop it again; women who experienced placental abruption, foetal growth impairment, etc. are also more likely to experience preeclampsia in subsequent pregnancies. Recent studies have demonstrated that these pregnancy-specific issues have a lasting impact on mother health, even after the index pregnancy. It has been determined that women who have experienced unfavourable pregnancy outcomes in the past are more vulnerable to metabolic and cardiovascular illnesses in the future. An elevated risk of vascular illness in later life is linked to maternal vascular, metabolic, and inflammatory pregnancy problems, according to growing data. For instance, it has been noted that mothers who suffered several problems or delivered very low birthweight babies were at several times higher risk of dying from cardiovascular reasons. [5,6] The fascinating possibility that pregnancy problems can predispose moms to subsequent vascular and metabolic disorders was covered by Sattar and Greer in 2005. [7]

Pre-eclampsia:

Pre-eclampsia is a significant illustration of a risk marker for noncommunicable diseases in later life. Since Corwin's 1927 description of the link between preeclampsia and subsequent cardiovascular disease (CVD), there has been a great deal of attention on this relationship as interest in women's CVD prevention has grown. [2,8]

Globally, one of the main causes of maternal and neonatal death is hypertensive disorders of pregnancy. Preeclampsia is a condition of pregnancy linked with new-onset hypertension and generally proteinuria; it usually develops after 20 weeks of gestation and often occurs near term. It might have severe characteristics or not. This condition is a spectrum of hypertensive disease in pregnancy that starts with prenatal hypertension, develops severe characteristics, and finally results in its more severe manifestations, which include HELLP syndrome and eclampsia. [14] This illness accounts for between 2 and 8% of pregnancy-related problems, over 50,000 maternal fatalities, and over 500,000 foetal deaths globally.[15] Through symptomatic therapy and delivery planning, problems for both mothers and newborns can be avoided with early diagnosis and appropriate management.

The majority of internal medicine, family medicine, and cardiology doctors did not inquire about the possibility of unfavourable pregnancy outcomes when screening for cardiovascular risk factors, according to a survey conducted in 2021 of doctors. Additionally, these doctors were not familiar with the guidelines set forth by the American Heart Association and the American College of Obstetricians and Gynaecologists regarding the treatment and follow-up of women who have pre-eclampsia. [9] Knowledge gaps in risk assessment and screening after unfavourable pregnancy outcomes have also been found in other research. [4,10] This results in the loss of important chances for risk reduction and postnatal counselling, as well as prospective chronic disease screening in the years that follow. Sattar N et al [7] proposed that maternal vascular risk factors, which may be "modifiable" prior to conception, are associated with a higher risk of preterm delivery and low birth weight, and that difficulties connected to pregnancy and coronary heart disease may have similar disease pathways. Similarly, Magnussen et al. [11] postulated that a higher incidence of preeclampsia was linked to cardiovascular risk factors that existed years before to pregnancy.

On the other hand, other researchers linked placental dysfunction, commonly referred to as "Placental syndrome," to poor pregnancy outcomes as well as an increased risk of vascular and metabolic illnesses in later life. A range of pregnancy issues, including as preeclampsia, intrauterine growth restriction, preterm labour, premature rupture of the membranes, late spontaneous miscarriage, and abruptio placentae, were proposed to be linked to faulty deep placentation in 2010 by Bronsens et al. [12]. Targeted biopsies were frequently used to explore the placental vascular bed pathology that was the cause of these problems. These researchers summarized the key varieties of deep placentation defects by closely evaluating the biopsy technique in their published evaluation. Based on the degree of remodelling limitation and the existence of obstructive lesions in the myometrial portion of the spiral arteries, they developed criteria for the classification of faulty deep placentation into three kinds [12]. The major obstetric syndromes, such as preeclampsia, foetal growth restriction, and spontaneous preterm labour brought on by impaired placental bed spiral artery remodelling, may be the consequence of the uterus's impaired functional maturation during the early stages of reproduction, according to a 2015 study by Bronsens et al. [13]

According to recent studies, Asians may not be at high risk and that morbidity is higher in poor nations, especially in Africa and Latin America. [16,17] Comparatively to Native Americans, Black Americans, and Europeans, patients from China, New Zealand, and Asian America have a lower incidence of preeclampsia, according to other studies that have documented similar findings. [18-20] Preeclampsia has a number of risk factors and predeterminants. Preeclampsia is linked to a number of risk factors, such as a history of chronic hypertension, diabetes mellitus, renal disease, obesity, short stature, nutritional deficiencies, gestational hypertension in prior pregnancies, hydatidiform mole, multiple pregnancies, foetal macrosomia, nulliparity, advanced maternal age, high body mass index, and assisted reproduction. [20-23]

Future pregnancies carry a considerable chance of preeclampsia recurrence. Preeclamptic pregnant women are more likely to develop persistent hypertension, cardiovascular disease, and stroke in their lives. The risk is correlated with the gestational age at the time of beginning and the severity of the hypertension condition during pregnancy. When describing the severity of the condition in connection to the requirement for an iatrogenic birth before 37 weeks or the time of diagnosis at or before 34 weeks of gestational age, the words "preterm" or "early-onset" preeclampsia are employed. Compared to late-onset

preeclampsia, whose pathophysiology is more closely linked to endothelial dysfunction predisposing cardiovascular or metabolic hazards, early-onset preeclampsia is particularly associated with poor placentation, foetal growth limitation, and worse long-term maternal cardiovascular outcomes.

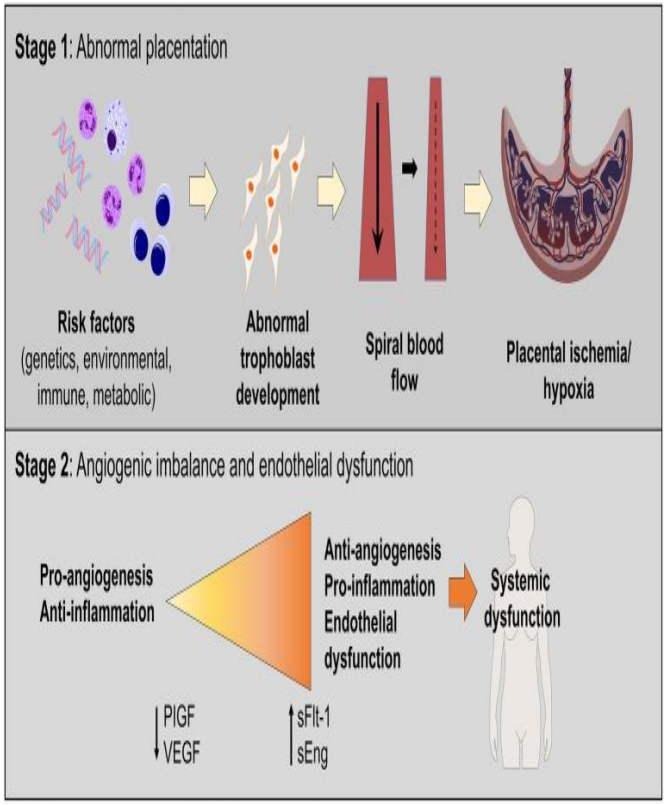

Figure 1: Pathophysiology of preeclampsia (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10060641/)

Cowin and Herrick's 1927 publication [12] was one of the first to identify the possibility of maternal heart illness in later life. According to a study by Irgens et al. [24], women who experienced preeclampsia during their pregnancy and gave birth prematurely were eight times more likely to die from cardiovascular disease (CVD) than women who did not experience preeclampsia and gave birth on schedule. The 626,272 infants that were the mothers' first deliveries between 1967 and 1992 were all analyzed by the authors, who separated the parents and mothers into two cohorts according to whether the mother experienced preeclampsia throughout her pregnancy. Because preterm pregnancies may result in more severe cases of preeclampsia, the subjects were further categorized based on the term or preterm birth.

Preeclamptic women were 1.2 times more likely to die over the long term than non-preeclamptic women. Pregnant women who experienced a preterm delivery were 2.71 times more likely to have a preterm delivery than preeclamptic women whose pregnancies ended at term. Specifically, there was an 8.12-fold increased risk of cardiovascular death in women who had both preterm birth and preeclampsia. Preeclampsia may be associated with hereditary variables that raise the risk of cardiovascular disease, according to the authors' conjectures. Wilson et al. investigated the link between the development of circulatory disorders later in life and hypertensive conditions of pregnancy, such as preeclampsia and gestational hypertension. [25] They matched two comparison groups: 1200 women with gestational hypertension and 1200 women without a history of raised blood pressure, with a cohort study of 1200 women who experienced preeclampsia during their first singleton pregnancy. In every metric, there were noteworthy positive correlations between gestational hypertension or preeclampsia/eclampsia and subsequent hypertension. The authors came to the conclusion that hypertensive disorders of pregnancy that developed later in life were linked to hypertension-related diseases, and that a fuller understanding of this relationship should result in earlier diagnosis and better therapy, as well as a decrease in the morbidity and mortality from these diseases.

Table 1:

Author	Study	Description
Ferreira RC, et.al (2020) [29]	Systematic review	Found that after pre-eclampsia, there is a 75% increased chance of getting CKD (HR 1.82 [95% CI: 1.27–2.62]) and a 3-fold higher chance of end-stage renal disease (HR 3.01 [95% CI 1.92–4.70]).
Grandi SM et.al (2019) [27]	Systematic review	showed that for moderate pre-eclampsia (odds

		ratio [OR] 2.24 [1.72–2.93]), the risk of cardiovascular morbidity increases by a factor of two, and for severe pre-eclampsia (OR 2.74 [2.48–3.04]), it increases by a factor of more than 2.5.
Basit S (2018) [28]	Cohort study	The likelihood of acquiring vascular dementia after pre-eclampsia was shown to be three times higher in a recent cohort research with over a million individuals (hazard ratio [HR] 3.46 [95% CI 1.05–1.99]). When, comparing early-onset (<65 years old) to late-onset (≥65 years old) vascular dementia, this connection was larger.
Brouwers L et.al (2018) [30]	Systematic review and meta-analysis	Women with a history of pre-eclampsia are more likely to get venous thromboembolism (VTE) in the future.
Wu et.al (2017) [26]	Systematic review	A pre-eclampsia history increases the risk of ischemic heart disease in the future by two times (risk ratio [RR] 2.11 [95% CI: 1.60–2.77]). a 71% higher risk of stroke (RR 1.71 [95% CI: 1.38–2.11]) and a 3.5-fold increased risk of heart failure (RR 3.62 [95% CI: 2.25–5.85]) The adjusted risk ratio (aRR) for coronary heart disease (CHD), heart failure, stroke, and CVD death was higher in the first ten years after the impacted pregnancy than it was in the years after the pregnancy.
Bellamy L (2007) [32]	Systematic review And meta-analysis	examined a dataset of 3,488,160 women, 198,252 of whom had a history of preeclampsia. The results showed that after 14.1 years of weighted mean follow-up, the relative risk of hypertension for women with a history of preeclampsia was 3.70 (2.70 to 5.05), for ischemic heart disease it was 2.16 (1.86 to 2.52), for stroke it was 1.81 (1.45 to 2.27), and for venous thromboembolism, 1.79 (1.37 to 2.33) after 4.7 years. After 14.5 years, the relative risk of overall death following preeclampsia was 1.49 (1.05 to 2.14). The authors hypothesized that

		there may be a shared cause of preeclampsia and cardiovascular disease in women, that preeclampsia influences the development of the disease, or both.
Kestenbaum B et.al (2003) [31]	Retrospective cohort study	After experiencing severe pre-eclampsia, almost 30,000 women had a two-fold greater risk of being hospitalized with VTE up to 10 years after giving birth (adjusted hazard ratio [aHR] 2.3 [95% CI: 1.3–4.2]).

A meta-analysis of five case-control and ten cohort studies a total of 116,175 women with and 2,259,576 women without preeclampsia/eclampsia was carried out by McDonald et al. [33] According to a 2004 study by Haukkamaa et al., [34] a history of preeclampsia was found to be an independent risk factor for subsequent coronary artery disease in 141 parous women who were relatively young (less than 66 years old) and had coronary artery disease as established by angiographical means. At one year postpartum, Smith et al. [35] prospectively evaluated biochemical and physical cardiovascular risk factors in a group of women who developed preeclampsia and in a control group. According to Melchiorre et al., [36] the severity of preeclampsia, the onset of gestational complications, the need for an iatrogenic preterm birth, the association with intrauterine foetal growth restriction (FGR), and the number of gestations affected by hypertensive disorders of pregnancies (HDPs) all influence the long-term risk of developing chronic hypertension.

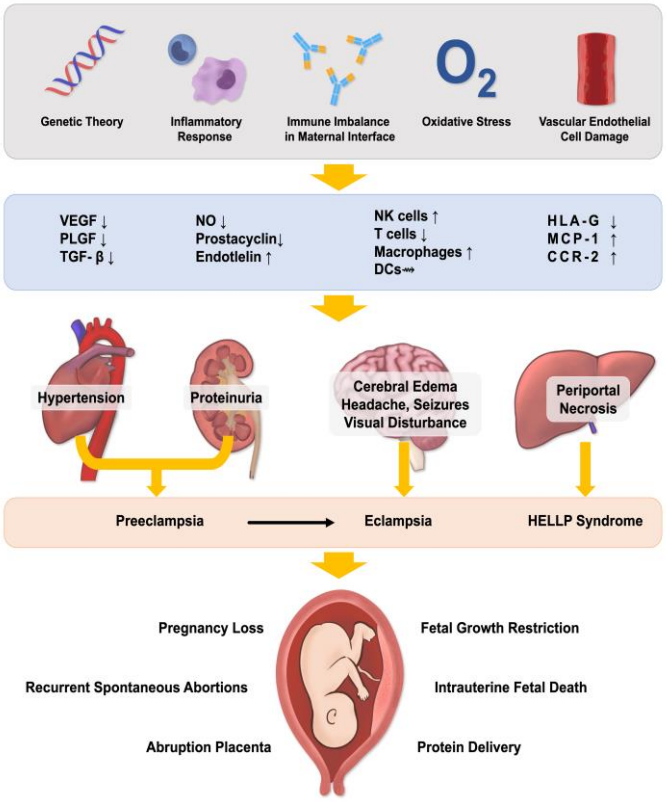

Figure 2: Mechanism of preeclampsia (https://www.imrpress.com/journal/CEOG/49/8/10.31083/j.ceog4908170/htm)

Gestational hypertension

The International Society for the Study of Hypertension in Pregnancy defines gestational hypertension as new onset hypertension (SBP >/= 140 mmHg or DBP >/= 90 mmHg) after 20 weeks of gestation without pre-eclamptic symptoms. [37] The pathogenesis of essential hypertension is complicated and multifaceted. These include the effects of obesity, insulin resistance, and sleep apnoea, if they are present as comorbidities, as well as heredity, environment, sex and ethnicity, vascular, renal, hormonal, and sympathetic nervous system mechanisms.[38]

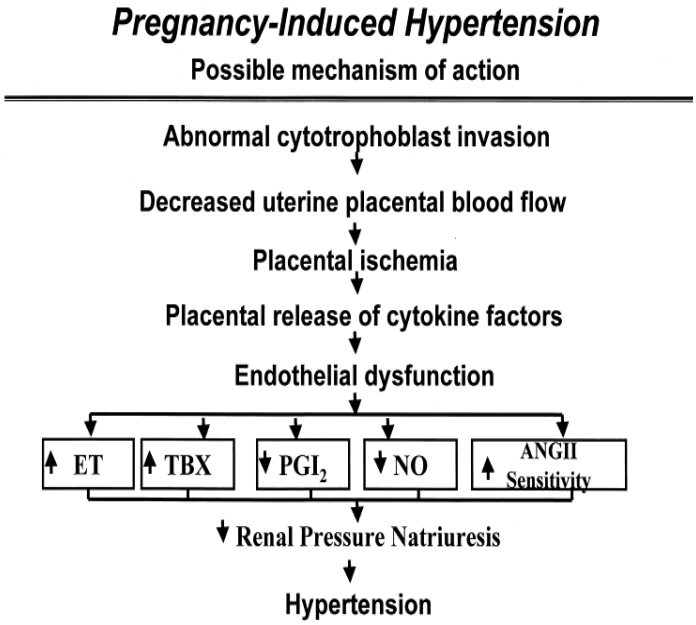

Figure 3: Pregnancy induced hypertension (https://www.sciencedirect.com/science/article/abs/pii/S0895706101020866)

Table 2:

Author	Study	Description
Grandi et al (2019) [39]	systematic review and meta-analysis (pooled data of nine cohort studies)	Found that the risk of cardiovascular morbidity, such as coronary artery disease, myocardial infarction, coronary revascularization, peripheral arterial disease, transient ischemic attack, and stroke, is 67% higher when gestational hypertension is examined separately from preeclampsia (pooled OR 1.67 [95% CI: 1.28–2.19]).14 After sensitivity analysis that removed studies with composite outcomes, this climbed to an 87% greater risk and decreased between-study heterogeneity (OR 1.87; 95% ICI: 1.55–2.25; I2: 60.6% vs. 83.9%).14 Cerebrovascular morbidity alone was associated with a 41% increased risk (pooled OR 1.41 [95% CI: 1.31–1.52]).

Women who experienced prenatal hypertension (GH) without proteinuria are at a similar risk of developing cardiovascular disease (CVD) and chronic hypertension as women who have late-onset or term preeclampsia [41]. An increased risk of diabetes mellitus or renal damage is linked to gestational hypertension [40]. The entire HDP burden reported as incidence per woman is significantly higher than that expressed as incidence per pregnancy, as demonstrated by Garovic et al. [42] in 2020. By focusing solely on hypertension during pregnancy, the number of women who suffer from this illness and may be at risk of developing cardiac or kidney problems in the future is underestimated. A more accurate evaluation of women who have had multiple pregnancies is possible by looking at the per-woman rate, as some women may have experienced hypertension during one pregnancy but not the other. [42]

Pre-term birth

A preterm delivery occurs when an infant is delivered before 37 full weeks of gestation. In many instances, the exact process underlying spontaneous preterm delivery remains unclear. The condition is believed to be brought on by a variety of circumstances, such as inflammation, immune-mediated processes, uterine overdistension, uteroplacental infection, ischemia or bleeding, and stress.[43] The pathway that connects spontaneous preterm delivery to subsequent CVD may involve inflammation, or the trigger event could be aberrant placentation. [44] Among other reasons, uncontrolled pre-eclampsia or hypertension, foetal development limitation, or placental abruption may need an iatrogenic preterm delivery.

Table 3

Author	Study	Description
Kessous et al (2013) [44]	Population based cohort study	evaluated the incidence of cardiovascular illness in a cohort of 47,908 women between 1988 and 1999 with follow-

		up until 2010, 5992 of whom (12.5%) delivered preterm (less than 37 weeks' gestation).
Robbins et.al (2014) [63]	Systematic review	compiled the findings of ten research evaluating the relationship between a history of PTB and the morbidity or death from CVD later on. Based on a review of five research, women with a history of postpartum hemorrhage (PTB) are twice as likely to die from cardiovascular disease (CVD) than women who gave birth on schedule. According to two studies, women who had at least two pregnancies that ended in PTBs were statistically significantly more likely to experience CVD-related morbidity and death outcomes (variously defined) than women who had at least two births but just one PTB.
Ngo et.al (2015) [45]	Popuation based record linkage study	During the study period, 59,563 women (7.5%) had at least one preterm birth. After adjustment for CVD risk
		factors other than smoking, adjusted hazard ratios (AHR) of CVD among women who ever had a preterm birth was 1.78 [1.61–1.96]. Associations were greater for extreme (AHR = 1.98 [1.63–2.42]) and moderate (AHR = 2.06 [1.69–2.51]) than late preterm birth (AHR = 1.63 [1.44–1.85]), for indicated (AHR = 2.04 [1.75–2.38]) than spontaneous preterm birth (AHR = 1.65 [1.47–1.86]), and for having ≥two (AHR = 2.29 [1.75–2.99]) than having one preterm birth (AHR = 1.73 [1.57–1.92]). A further correction for maternal smoking weakened, but did not remove the correlations. Additionally, there was an independent correlation found between smoking during pregnancy and the risk of CVD in mothers. .
Catov et al (2016) [46]		revealed that, regardless of their pre-pregnancy metabolic status and pregnancy difficulties, women with a

		history of preterm birth were more likely to develop metabolic syndrome than women who delivered their babies on time.
Pariente et al. (2017) [47]		found that there was a higher chance of long-term maternal kidney damage in women who had preterm deliveries (PTD).

Whether due to spontaneous birth or medical intervention, the risk of composite cardiovascular morbidity (OR 1.63 [95% CI: 1.39–1.93]), [27] CHD (RR 1.49 [95% CI: 1.38–1.60]), and stroke (RR 1.65 [95% CI: 1.51–1.79]) is 1.5 times higher when a premature infant is delivered. [26, 43] While spontaneous preterm delivery is still an independent risk factor for future maternal cardiovascular disease when cardiovascular risk variables are taken into account, iatrogenic preterm delivery has a greater correlation with future all-cause mortality. [47–50]

Gestational diabetes

Changes in insulin sensitivity are a result of the body adjusting to a typical pregnancy. Early in pregnancy, there is an increase in insulin sensitivity, which encourages the intake of glucose to store energy for later in pregnancy. [51] Increases in placental and local hormones lead to a shift toward insulin resistance as pregnancy goes on. [51] To encourage the transport of glucose to the developing fetus, blood glucose levels are slightly raised. [51] Increased glucose-stimulated insulin production and pancreatic B-cell enlargement and hyperplasia are responsible for maintaining glucose homeostasis. [51] In about 80% of cases of GDM, chronic insulin resistance combined with the natural insulin resistance of pregnancy results in beta-cell malfunction. [51] Because of their comparable pathophysiologies, T2DM and this condition may belong to the same illness spectrum. This has been debated. Other reasons and developing autoimmune diabetes are blamed for the other instances. When compared to normoglycemic pregnancy, GDM is linked to an almost ten-fold increased chance of developing T2DM (RR 9.51 [95% CI: 7.14–12.67]). Any type of diabetes increases the risk of CVD. This is because obesity, dyslipidemia, and hypertension are frequently present, and chronic inflammation that causes thrombosis has an adverse effect on the vascular.

A two-fold increased risk of future cardiovascular events (RR 1.98 [95% CI: 1.57–2.50]), a five-fold increased risk of coronary artery disease (aRR 1.59 [1.30–1.94]), and an 85% increased risk of composite cardiovascular morbidity and mortality (OR 1.68 [95% ICI: 1.11–2.52]) are all associated with GDM. Additionally, there is a 25% significant increase in the risk of stroke (OR 1.25 [95% CI: 1.07–1.48). [52–55]

Author	Study	Description
Barrett PM (2020) [56]		A higher chance of developing CKD exists for black women with a history of GDM (aRR 1.78 [95% CI: 1.18–2.70]). Compared to white women, black women are more likely to develop chronic kidney disease (CKD) and to see their disease progress to end-stage renal disease. This risk may be exacerbated by GDM, albeit the exact mechanism is unknown.
Wang Y (2020) [57]	systematic review	demonstrated a substantial correlation between GDM and the following cancers: liver

		(RR 1.27 [95% CI: 1.03–1.55], stomach (RR 1.43 [95% CI: 1.02–2.00]), and thyroid (RR 1.28 [95% CI: 1.16–1.42]).37 T2DM also dramatically raises the incidence of stomach and thyroid cancer, suggesting a shared underlying mechanism. Greater study populations and longer follow-up periods may reveal connections to additional malignancies.
Azami et al (2019) [58]	systematic review and meta-analysis	(95% CI: 1.22–2.07) with RR of 1.59. Chronic inflammation, disruption of the hypothalamic-pituitary-adrenal axis, abnormal serotonin regulation, and the stress of receiving a chronic illness diagnosis are some of the hypothesized processes that may connect the illnesses.
Huang et al (2016) [59]	meta-analysis of prospective cohort studies	Individuals with HbA1c of 39 mmol/mol or fasting glucose concentrations as low as 5.6 mmol/L were shown to be at higher risk for health problems. An elevated risk of coronary heart disease and composite cardiovascular disease was linked to increases in HBA1c to 39–47. Women who have had GDM should be followed up with in order to facilitate early diagnosis and preventive actions, as this lowers the likelihood of problems.
Bellamy et al. (2009) [64]	systematic review and meta-analysis	They found that women who developed gestational diabetes had a higher chance of getting type 2 diabetes (RR 7.43, 95% CI 4.79–11.51) compared to women who had a norm-glycaemic pregnancy.
. Göbl et al (2011) [60]		The best indicators of acquiring diabetes after GDM were found to be older than 35 years old, decreased glucose tolerance, and HDL cholesterol levels less than 50 mg/dL.

		These findings were based on a yearly follow-up of women with a history of GDM for a maximum of 10 years. In addition, women who have had a previous diagnosis of GDM are more likely to develop metabolic syndrome in the future. This is a group of metabolic disorders that include obesity, dyslipidemia, DM, and hypertension, all of which raise the risk of cardiovascular disease.
Valizadeh et al. (2015) [61]		Twenty-two women (20%) developed metabolic syndrome, eleven (10%) had impaired glucose tolerance or impaired fasting glucose, and thirty-six (32.7%) acquired type 2 diabetes.

The authors recommended routine screening for diabetes and other cardiovascular risk factors in women with a history of GDM. Endothelial dysfunction and cardiovascular disease are at risk for developing in people with gestational diabetes mellitus (GDM). Pregnancy complicated by GDM or even before may cause blood vessel damage that raises the risk of cardiovascular disease in the future. In a recent study, arterial stiffness was assessed in 29 pregnant women (13 with GDM and 16 with an uncomplicated pregnancy at 28 ± 2 gestational weeks). When compared to women with simple pregnancies, women with GDM had a distinctive flattened tissue oxygen saturation index curve, which indicated changes in muscle oxygenation and microvascular reactivity. [62]

Conclusion

It is evident that a higher risk of long-term maternal morbidity is linked to numerous obstetric problems. Most of them, if not all of them, are probably caused by similar predisposing factors in these women. Women themselves and the medical staff who care for them need to be aware of these dangers in order to improve women's health and reduce such risks. It seems that a variety of therapies, such as dietary changes, weight loss, and greater physical exercise, can reduce these risks. Women should be encouraged to breastfeed for a number of reasons.

A substantial amount of research indicates that unfavourable pregnancy outcomes may serve as sentinel events for chronic illness in the future in women.

Mothers who experience pregnancy-related problems such as gestational diabetes mellitus, preeclampsia, or gestational hypertension are more likely to acquire diabetes and/or cardiovascular disease later in life. It is advised that women who experienced this kind of pregnancy-related syndrome change their diet and exercise routines after giving birth. It is advised to examine plasmatic glucose levels and blood pressure in order to minimize long-term morbidity by early treatment action.

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