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A REVIEW ON LONG TERM EFFECTS OF PREECLAMPSIA, GESTATIONAL DIABETES AND THEIR MANAGEMENT IN PREGNANCY

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ABSTRACT

Most pregnancy-related complications appear to resolve at delivery or shortly thereafter. Common examples are preeclampsia and gestational diabetes. Women who developed such complications are known to be at increased risk of developing similar complications in future pregnancies. It has recently become evident that these women are at an increased risk of long term medical complications. A search through scientific publications in English regarding the association of obstetric complications and long-term maternal illness, there is a clear association between various obstetric complications and long-term effects on maternal health. Women with a history of adverse pregnancy outcomes are at increased risk of cardiovascular and metabolic diseases later in life. Data increasingly links maternal vascular, metabolic and inflammatory complications of pregnancy with an increased risk of vascular disease in later life.

KEYWORDS: Pregnancy complications; long-term effects; gestational diabetes; preeclampsia.

INTRODUCTION

Most pregnancy related medical complications appear to resolve at delivery or shortly thereafter. Common examples are placental abruption, preeclampsia and gestational diabetes. Women who developed gestational diabetes (GDM) are likely to develop it again, as are women who experienced placental abruption, fetal, fetal growth impairment, etc. Recently,

research has shown that these pregnancy-specific complications continue to affect maternal health long a13fter the index pregnancy. It has become apparent that women with a history of adverse pregnancy outcome are at increased risk of cardiovascular and metabolic diseases later in life. For example, it has been reported that women who gave birth to very low birth weight babies or experienced combined complications had a several-fold increased risk of mortality from cardiovascular causes.[1,2]

They debate whether it was the pregnancy that had this long-term effect on maternal health, or it was the result of predisposing maternal conditions which were expressed during pregnancy and eventually caused chronic morbidity. Researchers who believe the latter coined the phrase, "pregnancy as a stress-test". In 2005, Sattar and Greer reported on the intriguing probability that complications in pregnancy also predispose mothers to latter vascular and metabolic disease.[3] They suggested that pregnancy complications and coronary heart disease may have common disease mechanisms and that maternal vascular risk factors, potentially "modifiable" before pregnancy, correlated with increased risk of preterm delivery and low birth weight. Similarly, Magnussen et al. hypothesized that cardiovascular risk factors that were present years before pregnancy were associated with increased risk of preeclampsia.[4] Conversely, other researchers associated adverse pregnancy outcome, as well as the increased risk of vascular and metabolic disease in later life, with placental malfunction, also known as "Placenta syndrome". For example, in 2010 Bronsens et al. suggested that defective deep placentation was associates with spectrum of pregnancy complications including preeclampsia, intrauterine growth restriction, and preterm premature rupture of membranes, late spontaneous abortion and abruption placentae. The placental vascular bed disease that underpinned these complications was commonly investigated with targeted biopsies. In their published review, these researchers critically evaluated the biopsy technique to summarize the salient types of defective deep placentation. They proposed criteria for the classification of defective deep placentation into three types, based on the degree of restriction remodeling and the presence of obstructive lesions in the myometrial segment of the spiral arteries.[5] In the 2015 Bronsens et al. suggested that the major obstetric syndromes, including preeclampsia, fetal growth restriction and spontaneous preterm labor caused by impaired placental bed spiral artery remodeling may be the result of impaired functional maturation of the uterus during the early reproduction years.[6] More recently, IIekis et al. published a summary of an executive workshop of the Eunice Kennedy Shriver National Institute of Child Health and Human Development on placental origins of adverse

pregnancy outcomes-potential molecular targets.[7] According to the researchers, much progress was made in understanding the molecular pathways in the placental involved in the pathophysiology of pregnancy-related disorders. Utilization of this information could assist in the development of new drug therapies to improve pregnancy outcome, both prevention and treatment of disorders including preeclampsia, fetal growth restriction and uterine inflammation.

Regardless of whether long-term maternal complications were caused by pregnancy or first recognized during pregnancy, this review summarizes current information regarding the association between the most common obstetric complications-gestational diabetes, preeclampsia and their long-term maternal effects.

Complications

Complications of pregnancy are health problems that are related to pregnancy. Factors increasing the risk of pregnancy complications beyond the normal level of risk may be present in the pregnant individual medical profile either before they become pregnant or during the pregnancy. These pre-existing factors may relate to the individual's genetics, physical or mental health, their environment and social issues or a combination of those. The complications observed in pregnancy are:

- **Gestational diabetes:** Gestational diabetes is when a woman without diabetes develops high blood sugar levels during pregnancy.
- **Preeclampsia:** Gestational hypertension, proteinuriea (>300mg) and edema. Severe preeclampsia involves a BP over 160/110. It affects 5-8% of pregnancies.
- **Anemia:** Levels of hemoglobin are lower in the third trimesters. Anemia prevalence during pregnancy differed from 18% in developed countries to 75% in South Asia.
- **Hypothyroidism:** Hypothyroidism an autoimmune disease that affects the thyroid in pregnant individuals i.e. the increasing of TSH levels.

Gestational diabetes mellitus

When women with history of gestational diabetes (GDM) undergo the 75 gram glucose tolerance test (GTT) at 6-12 weeks postpartum, 2-16% are diagnosed with type 2 diabetes (DM) and 36% are found to have intolerance to carbohydrates. Women who had prior GDM have a 36-70% risk of developing type 2 DM later in life, depending on risk factors and length to follow – up. It is important for women who had GDM to have appropriate follow up since, over time, often before patients are diagnosed, DM causes damage to various organs

(heart, blood vessel, kidney, eyes, nerves, etc.) Despite the deceptively benign term, "intolerance to carbohydrates, this condition is associated with significant morbidity. In the 2012 Lee et al. performed a Meta – analysis that induced 15 prospective studies with 760,925 participants and reported that pre – diabetes, defined as impaired glucose tolerance or a combination of impaired fasting glucose and impaired glucose tolerance, were associated with an increased risk of stroke.[8] Huang et al. performed a Meta - analysis of prospective cohort studies to evaluate the associations between pre-diabetes, defined as impaired glucose tolerance, impaired fasting glucose, or raised HbA1c, and the risk of cardiovascular disease and all-cause mortality.[9] Their analysis included 53 prospective cohort studies with 1,611,339 individuals. The median follow-up duration was 9.5 years. Compared with normal – glycaemia, prediabetes was associated with an increased risk of composite cardiovascular disease, stroke, and all-cause mortality. The health risk was increased in people with fasting glucose concentrations as low as 5.6 mmol/L or HbA1c of 39 mmol/mol. Increases in HbA1c to 39 -47 were associated with an increased risk of composite cardiovascular disease and coronary heart disease. Follow-up of women who had GDM enables preventive measures and early diagnosis; early detection of DM decreases the risk of complications.[10]

In 2009 Bellamy et al. published a comprehensive systematic review and Meta –analysis to assess the strength of association between GDM and the risk of developing type 2 DM and the effect of factors that might modify the risk of patient age older than 35 years were identified as the best predictors of developing diabetes after GDM. In the 2015 Valizadeh et al. also studied risk factors and incidences of abnormal glucose levels and metabolic syndrome in 110 women with history of GDM one to six years after their pregnancy.[11]

Women previously diagnosed with GDM are also at increased risk of future metabolic syndrome, a combination of metabolic abnormalities that include hypertension, DM, Dyslipidemia, and obesity, all of which increases the risk of cardiovascular disease. Lauenborg et al. studied the prevalence of metabolic syndrome using three different criteria – World Health organization 1999 (WHO), The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and treatment of high blood cholesterol in adults 2001, and European Group for the study of insulin resistance 2002 – among 481 Danish women with previous diet – treated GDM. Follow up occurred at a median of 9.8 years after pregnancy.[12] Valizadeh et al. also studied risk factors and incidences of abnormal glucose levels and metabolic syndrome in 110 women with history of GDM one to six years after

their pregnancy. 32.7% developed type 2 diabetes, 10% had impaired fasting glucose or impaired glucose tolerance and 20% developed metabolic syndrome.[13] The authors suggested that women with a history of GDM should be screened at regular intervals for diabetes and other cardiovascular risk factors.

GDM is a risk factor for the development of endothelial dysfunction and cardiovascular disease. It is possible that damage to blood vessels that increases the risk of future cardiovascular disease develops during pregnancy complicated by GDM or even prior to it.[14] Kessous et al. reported an association between GDM and maternal cardiovascular morbidity.[15] It appears that a high glucose level during pregnancy, if within the range of slight glucose intolerance, may serve as a marker for future maternal atherosclerotic morbidity. Charach et al. studied 815 women who delivered between the years 2000-2012 who had at least one glucose measurement during pregnancy and subsequently developed atherosclerotic morbidity.[16] Gestational diabetes is also associated with an increased risk of future renal morbidity. A population based study compared the incidence of renal morbidity in a cohort of 97,968 women of whom 9542 (9.7%) had at least one previous pregnancy complicated by GDM.[17] Beharier et al. reported that GDM was also a significant risk factor for long term ophthalmic morbidity.[18] The authors of another study reported that women who developed GDM rarely followed the recommended dietary and physical activity in the postpartum period. The authors stated that women with GDM face lifelong increased risk for subsequent diabetes; primarily type 2 DM. Timely testing for prediabetes may provide an opportunity for ob-gyns to prevent or delay the onset of type 2 DM through diet, physical activity, weight management and pharmacologic intervention.[19]

S.NO	Investigations	Normal values	
1.	GCT(mg/dl)	More than 140	
2.	GTT(mg/dl)		
	1)FBS	2)1hr after glucose administration	3)2hr after glucose administration
	>92mg/dl	>180mg/dl	>153mg/dl
3.	Pre-diabetic(mg/dl)	101-125(in fasting condition)	141-200(post meals)
4.	Diabetes(mg/dl)	125mg/dl and above (in fasting condition)	200 and above (post meals)

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ob-gyns to prevent or delay the onset of type 2 DM through diet, physical activity, weight management, and pharmacologic intervention.

Management

Non pharmacological treament:

1. Exercise or walking.
2. Medical nutrition therapy.
3. Diet therapy.[20]

Pharmacological treatment

When medical Nutritional therapy (MNT) alone fails, pharmacologic therapy is indicated. AACE guidelines recommend INSULIN as the optimal approach. INSULIN therapy is required for the treatment of DM during pregnancy. METFORMIN and the SULPHONYL UREA GLYBURIDE are the 2 most commonly prescribed oral anti hyper glycemic agents during pregnancy. METFORMIN started at 500mg_OD or BD daily and increased over 2 weeks as needed to a maximum dose of 2500mg daily. Supplemental INSULIN eventually required 46% of METFORMIN patients. INSULIN requirement _0.6, 0.7, 0.8 units /kg/day-1st, 2nd, 3rd trimesters. Given as 2 injections /day(some require 3-4 injections.[21] GLYBURIDE (micronized tablets) of 1.25,2.5, and 5mg strengths for oral administration. Usual starting dose of standard GLYBURIDE tablets is 2.5-5mg daily. (Micronized glyburide tablets: 1.5-3mg daily). Standard GLYBURIDE: Daily doses of more than 20 mg are not recommended. Micronized GLYBURIDE: Daily doses of more than 12mg are not recommended.[22]

Preeclampsia

Preeclampsia is one of the leading causes of morbidity and mortality worldwide. It is a pregnancy-specific multi-organ syndrome that affects 2-8% of pregnancies. It is a condition of placental pathogenesis with acute onset of predominantly cardiovascular manifestations attributable to generalized vascular endothelial activation and vasospasm resulting in hypertension and multi-organ hypo-perfusion. It is defined as a new onset of a multisystem pregnancy-related disorder that includes hypertension and either proteinuriea or end-organ dysfunction, identified after 20 weeks gestation. During the index pregnancy, preeclampsia causes multi-system damages due to microangiopathy that lead to maternal morbidity that may include cardiac and renal failure, liver damage, cerebrovascular bleeding, pulmonary edema, disseminated intravascular coagulopathy (DIC), placental ischemia, etc. The effects

on the fetus include prematurity (due to indicated preterm deliveries), fetal growth impairment and intrauterine fetal demise. After delivery, the disorder tends to resolve in the majority of women although some remain hypertensive. There is a significant risk of preeclampsia reoccurrence in future pregnancies. There is an increased life time risk of chronic hypertension, cardiovascular disease (CVD) and stroke in women who experienced preeclampsia during pregnancy. The risk is related to severity of hypertensive disorders during pregnancy and the gestational age at the time of onset. The terms "preterm" or "early onset" preeclampsia are used to delineate the severity of the disease in relation to need for iatrogenic delivery before 37 weeks or the time of diagnosis at or before 34 weeks of gestational age. Early-onset preeclampsia is especially associated with poor placentation, fetal growth restriction and worse longtime maternal cardiovascular outcomes than late onset preeclampsia, whose pathogenesis is more related to predisposing cardiovascular or metabolic risks for endothelial dysfunction.

One of the earliest publications that identified the risk of later-life maternal cardiac disease was published in 1927 by Cowin and Herrick.[23] More recently Irgens et al.[24] Reported that women who had preeclampsia during pregnancy that ended in preterm delivery had and eight fold higher risk of death from CVD compared with women who did not have preeclampsia and delivered at term. The speculated that genetic factors that increase the risk of cardiovascular disease may also be linked to preeclampsia. Wilson et al. studied the association between hypertensive disease of pregnancy and that development of circulatory diseases later in life.[25]

Similar to the long-term risks of maternal morbidity associated with other pregnancy complications, e.g., gestational diabetes is unknown, whether preeclampsia was actually the cause of increased risk of morbidity in these women or nearly identified women who had a prior increased risk of CVD morbidity researchers who believe in the former theory coined the expression, "maternal placental syndrome" (MPS), a term that combines various pregnancy complications (hypertensive disorders, placental abruption, placental infarction, etc.) that originated from "diseased placenta vessels", often in women who had metabolic risk factors for CVD (including obesity, pre pregnancy hypertension, diabetes mellitus and Dyslipidemia). Ray et al. conducted a population based retrospective coherence study of 1.03 million women, of whom 75,380 were diagnosed with a maternal placental syndrome, who were free from cardiovascular disease before their first documented delivery, in order to

assess the risk of premature vascular disease in women who had a pregnancy affected by maternal placental syndrome.[26] The authors concluded that hypertension during pregnancy was associated with increased CHD and stroke incidence in middle age, largely because such women also had hypertension in their 50s and 60s, which has a substantially greater effect on vascular disease risk then hypertension during pregnancy without hypertension later in life. In 2017 Auger et al. studied the association between recurrent preeclampsia and long-term cardiovascular hospitalization.[28] They defines the following as maternal placental syndrome, preeclampsia, gestational hypertension, placental abruption and placental infarction. Smith et al. calculated the cardiovascular disease risk estimates at 10- years, 30-years, and lifetime CVD risk at 1- year postpartum following a pregnancy with or without a preeclampsia.[27]

The cause of the association between preeclampsia and future risk of CVD is unknown. McDonald et al. investigated whether the increased risk of CVD in formerly preeclamptic women was related to albuminuria, a known cardiovascular risk factor that is part of the definition of preeclampsia and that often persist after delivery.[29] History of preeclampsia denotes risks of morbidity in other organ systems, as well. Aukes et al. reported that history of preeclampsia was a risk maker for early cerebro vascular damage.[30] They noted that formerly eclamptic women demonstrated cerebral white matter lesions (WMLs) several years following the index pregnancy. The pathophysiology might be related to the predisposition for cerebro vascular or cardiovascular disease in search women and /or the occurrence of posterior reversible encephalopathy syndrome while pregnant. In a Cox proportional hazards model, adjusted for confounders, a history of preeclampsia remind independently associated with ophthalmic complications. Postman et al. reported that women who experienced preeclampsia more frequently reported daily cognitive failures and showed increased emotional dysfunction several years later, but were not impaired on objective neuro cognitive testing.[31] Low birth weight is associated with increased rates of coronary heart disease, stroke, hypertension, and non- insulin-dependent diabetes during adult life. Mal-programming of the fetus may result from adaptations to a condition where placental nutrient supply fails to match fetal demand. In order to decrease the risks of long-term effects on the health of the women with history of preeclampsia, women with history of preeclampsia and the medical staff caring for them during the following years need to be familiar with these risks and act to modify them. Taylor et al. studied women risk perception for future cardiovascular disease after being diagnosed with a hypertensive disorder of pregnancy.[32] The authors concluded that although the majority of obstetrician-gynecologist was aware of

higher CVD risk after preeclampsia, weakness existed in the follow up care and counseling of these patients. These deficiencies would be amendable to directed educational activities to improve the implementation of current guidelines.

Management

All pregnant women should be screened for Preeclampsia at the first prenatal visit and periodically throughout the remainder of the pregnancy. Pregnant women with diastolic blood pressure of 105 to 110 mmHg or higher should receive Antihypertensive medication.[33] Women at increased risk for preeclampsia who have low calcium intake should increase their calcium intake. Antihypertensive drugs commonly used in the treatment of severe preeclampsia.[34]

Hydralazine (Apresoline)

Initial dose: 5mg –IV/10mg-IM.

When blood pressure is controlled repeat initial dose as needed (usually about every 3 hours; max: 400mg per day). If blood pressure is not controlled in 20 minutes, repeat initial dose every 20 minutes, until maximum dosage is reached, or go immediately to next step. If blood pressure is not controlled with a total of 20mg- IV or 30mg IM, consider using a different Antihypertensive drug (Labetolol+Nifedipine (Procardia), Sodium Nitroprusside (Nitropress).[35]

Labetolol (normodyne, trandate)

Initial dose: 20mg in IV BOLUS or 250mg-TID. If blood pressure is not controlled, give 40mg 10 minutes after initial dose and then 80 mg every 10 minutes for 2 additional doses (maximum 220 mg). If blood pressure is not controlled, use a different antihypertensive drug (HYDRALAZINE, NIFEDIPINE and SODIUM NITROPRUSSIDE).[36]

Methyldopa: Central and peripheral anti-adrenergic action.250-500mg-TID.[37]

Other Obstetric Complications

It is evident now that many additional obstetric complications associated with placental pathology result in an increased risk of long term maternal morbidity. For example, placental abruption, a condition associated with microvascular disturbance, was found to be associated with long term consequences for the mothers health. For more than 10 years, Pariental et. al followed 653 women who experienced placental abruption and reported that placental

abruption was a significant risk factor for long term cardiovascular disease.[38] Women with placental abruption in first pregnancy had increased risk of CVD death. Results were essentially unchanged by excluding women with pre-gestational hypertension, pre-eclampsia or diabetes. The increased risks were evident for ischemic hearts disease, acute myocardial infarction, hypertensive heart disease, non-rheumatic valvular disease, and congestive heart failure .On the other hand, Arazi et.al reported that placental abruption was not associated with an increased risk of long term renal morbidity.[39] Stillbirth and recurrent miscarriages may also be the result of placental pathology. Pariente et al. compared the incidence of long term atherosclerotic morbidity in a cohort of women with history of stillbirth.[40] After stillbirth; women had a significant higher cumulative incidence of cardiovascular and renal morbidity and cardiovascular and renal hospitalizations and had higher rates of simple and complex cardiovascular events.

As expected maternal obesity during pregnancy is also associated with an increased risk of various long term maternal morbidity. For example, Sasson et al. reported that obesity during pregnancy is an independent risk factor for long-term ophthalmic complications, and specifically diabetic retinopathy.[41] Obstetric complications were associated with long term risk of complications in the off spring. As mentioned previously, plentiful evidence links low birth weight due to intra uterine growth restriction and increased risk of vascular diseases in later adult life. This is considering being partly the result of programming through fetal nutrition.[42]

CONCLUSION

It is clear that many obstetric complications are associated with increased risk of long term maternal morbidity. It is likely that some, if not all, are due to common predisposing factors in these women. To improve women's health and decrease such risks, both women themselves and the medical team caring for them need to be aware of these risks. Multiple interventions including diet modifications, weight loss, and increased physical activity appears to be effective in decreasing these risks for a variety of reasons, women should be encouraged to breast feeding. Regarding prevention of long-term morbidity, Peters et al. reported that giving birth to more children was found to be associated with a higher risk of CHD later in life, whereas breastfeeding was associated with a lower CHD risk, women who both had children and breast feed had a non -significantly higher risk of CHD.[43] Moderate

intensity dancing was associated with reduced risk of CVD mortality to a greater risk than walking.[44]

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