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Review

Therapies for gestational diabetes and their implications for maternal and offspring health: Evidence from human and animal studies

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ABSTRACT

Obesity prior to and during pregnancy is associated with an increased risk of complications during pregnancy. One of the most common complications of pregnancy is gestational diabetes mellitus (GDM), a condition characterized by hyperglycemia and insulin resistance that is diagnosed in the third trimester of pregnancy. GDM predisposes both mothers and their children to increased obesity and cardiometabolic disorders, namely type 2 diabetes and cardiovascular disease. Current treatments include lifestyle changes and insulin injections, but oral anti-diabetic drugs such as metformin and glyburide are increasingly prescribed as they do not require injections. However, the long-term implications of therapies for diabetes during pregnancy on mothers and their offspring are not fully understood. In this review, we describe current treatments for GDM, including the first line lifestyle interventions such as exercise as well as insulin, glyburides and metformin. We also review selected natural health products that are sometimes used by individuals during pregnancy that could also be an effective therapeutic in pregnancies characterized by obesity or GDM. We focus on both the short- and long-term effects of treatments on the health of mothers and their offspring. We review the current literature from clinical research and animal studies.

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Abbreviations: GDM, gestational diabetes mellitus; T2D, type 2 diabetes; CVD, cardiovascular disease; DOHaD, developmental origins of health and disease; CDA, Canadian diabetes association; HOMA-IR, homeostatic model assessment for insulin resistance; DINT, dietary intervention; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1-α; mRNA, messenger ribonucleic acid; TGs, triglycerides; AKT, protein kinase B; ERK, extracellular signal regulated kinase; AMPK, 5′ adenosine monophosphate kinase; NICU, neonatal intensive care unit; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; GLUT1, glucose transporter 1; GLUT4, glucose transporter 4; Insig-1, insulin induced gene-1; PPAR-γ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; Vegf-A, vascular endothelial growth factor A; SOD, superoxide dismutase; PUFA, poly-unsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; SREBP-1c, sterol regulatory element binding protein 1; FAS, fatty acid synthase; SCD1, stearoyl-CoA desaturase 1; ACC1, acetyl-CoA carboxylase 1.

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1. Introduction

Throughout the world, more individuals have body mass indexes (BMI) that are classed as being overweight and obese. In fact, since 1975, worldwide obesity has almost tripled in the general population [1]. According to the World Health Organization, it is estimated that there are almost 2 billion overweight adults, including 650 million obese individuals. In addition, obesity is increasingly observed among children [1]. Currently, it is estimated that there are more than 41 million children either obese or overweight and based on current trends, it is anticipated that these numbers will continue to increase [1]. Obesity is a risk factor for type 2 diabetes (T2D), cancer, and cardiovascular disease (CVD). Of particular concern is that more than 300 million women are currently obese [1], which means that more women of childbearing age are at risk of developing gestational diabetes mellitus (GDM) [2]. In fact, around 60% of women of reproductive age are obese in the United States [3], while 1–14% of all pregnancies are affected by GDM, depending on the ethnicity and the diagnostic criteria used [4]. Furthermore, GDM incidence is increasing, which puts a greater burden on hospitals and the health care system to treat and prevent pregnancy-related complications in both mothers and their infants [5].

During pregnancy, blood volume increases [6], renal physiology changes [7], and drug metabolism is altered [8]. These are all factors that can influence the efficacy and dosage of various therapeutics and interventions. It is essential for clinicians and pharmacologists to understand these adaptations and how they are affected by pregnancy-related complications in order to limit negative health consequences and optimize benefits of therapies administered during pregnancy. While the decision to initiate drug therapy during pregnancy is a complex decision for women and their healthcare providers, avoiding treatment of the underlying pregnancy-related condition also carries risks for the health of the offspring. For example, GDM is associated with a higher incidence rate of obesity in the offspring [9,10]. The effect of interventions on the infant are sensitive to their timing. For example, an intervention administered in the first trimester of pregnancy is more likely to affect organogenesis compared to the third trimester. Interventions initiated in the third trimester could affect fetal weight, premature birth and delivery complications (Fig. 1). In addition, some medications or their metabolites may appear in the breast milk suggesting that transmission from mother to infant via the breastmilk could also influence health outcomes in these offspring. Thus, we reviewed articles which had stated the timing of their treatments to better understand when different interventions should be administered. The different studies and timings of treatments are summarized in Tables 1–3. This review will focus on standard treatments for GDM and their effects on both maternal and offspring health. We will begin by describing the relevance of the Developmental Origins of Health and Disease theory to the field. Next, the features of GDM are described with a thorough description of how GDM is managed. Then, lifestyle interventions such as calorie restriction and exercise prior to and during pregnancy will be presented. Afterwards, clinical and animal studies showcasing the effects of therapeutics, such as insulin, metformin and glyburide, on maternal and offspring health will be reviewed. And finally, we will address the growing use of natural health products during pregnancy and their effect on mothers and their offspring. The compounds that are reviewed include myoinositol, folate, omega 3 fatty acids, resveratrol, Vitamins C and E, and Vitamin D. Because each of these interventions for GDM are recognized to have both advantages and disadvantages, an important focus will be a critical review of the positive health benefits and potential adverse effects of these treatments on maternal and offspring health, including evidence from clinical studies and animal model experiments.

1.1. The developmental origins of health disease (DOHaD) theory

The Developmental Origins of Health and Disease theory, as described by Dr. Barker [11], defined that adverse intrauterine environments during fetal development influences the risk for chronic disease development in the offspring. These foundational studies focused on how maternal undernutrition predisposed the offspring to the development of obesity, cardiometabolic and CVD [11–13]. Dr. Barker's findings were based on hospital records from the early 1900s in England that showed an association between low birthweights and increased rates of cardiovascular disease and mortality later in the lives of both men and women [12,13]. On the other end of the spectrum, excess intake of caloric intake of fats and carbohydrates during pregnancy can also influence the development of metabolic disease in the offspring, supporting the DOHaD concept (recently reviewed in [14]). Frienkel was one of the first researchers to show a relationship between diabetes during pregnancy and fetal and infant health, a concept that he termed "fuel mediated teratogenesis" because the fetal environment that accompanies diabetes during pregnancy could alter the development of key organs involved in cardiometabolic health [15]. Since that time, epidemiological evidence and experimental data show a link between diabetes during pregnancy and a greater risk of cardiometabolic disease in the offspring as they age (reviewed in [16]). In addition, these prenatal factors can interact with the postnatal diet to influence disease risk. Consistent with the predictive adaptive response hypothesis, which has influenced the DOHaD hypothesis, the fetus adapts to the in utero environment through changes in gene expression that prepare the offspring for those same condi-

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