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Review Article

EFFECT OF POLYCYSTIC OVARY SYNDROME ON GESTATIONAL DIABETES MELLITUS AND INFERTILITY

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ABSTRACT

PCOS is a common endocrine disorder in women of childbearing age and approximately 3 – 26 % of Indian women are affected by PCOS and the worldwide prevalence is around 6 – 15 %. Many complications have been observed in PCOS women such as acquiring GDM and inability to conceive leading to infertility. The prevalence of GDM is higher in women with PCOS. This review article highlights in short the research findings during the last decade on the prevalence, diagnosis, outcome measures linking PCOS, GDM and Infertility in one platform to enable future research scholars, gynaecologists and laboratory personnel to develop new testing strategies to bring out better health care for women with PCOS.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is of clinical and public health importance as it is very common, affecting up to one in five women of reproductive age. It has significant and diverse clinical implications affecting reproductive status such as, infertility, hyperandrogenism and hirsutism; metabolic disturbances ranging from insulin resistance (IR), impaired glucose tolerance and type 2 diabetes mellitus (T2DM) together with an adverse cardiovascular risk profiles and psychological features comprising increased anxiety, depression and worsened quality of life. Gestational Diabetes Mellitus (GDM) is common with onset or first recognition during pregnancy. Various studies suggest that PCOS and infertility are associated with an increased GDM risk. This review article highlights the research findings during the last decade in the relevant field stressing the importance of a comprehensive evidence-based guidelines to aid early diagnosis with appropriate investigations for regular screening and treatment of these common conditions.

PCOS and GDM

PCOS is a common endocrine disorder in women of childbearing age. Women with PCOS demonstrated a significantly higher risk of developing GDM, pregnancy-induced hypertension (PIH), preeclampsia, preterm birth, caesarean section compared to controls. Their babies had a marginally significant lower birth weight and higher risk of admission to Neonatal Intensive Care Unit (NICU) compared to controls. Women with PCOS have increased risk of adverse pregnancy and neonatal complications. It is necessary to establish guidelines for supervision during pregnancy and parturition to prevent these complications (Jun Z Qin *et al*, 2013). PCOS is the most common endocrinological disorder affecting 4–12% of women (Hany Lashen, 2010). Modest weight loss of 5% to 10% of initial body weight has been demonstrated to improve many of the features of PCOS. Monitoring and management of long-term metabolic complications is also an important part of routine clinical care (H Teede, 2010).

GDM is any degree of glucose intolerance with onset during pregnancy and is associated with increased feto-maternal morbidity as well as long-term complications in mothers and offspring. Women detected to have diabetes early in pregnancy receive the diagnosis of overt, non-gestational diabetes. GDM is diagnosed by an Oral Glucose Tolerance Test (OGTT) or fasting glucose concentrations. Approximately 7% of all pregnancies are complicated by GDM, resulting in more than 200,000 cases annually. The prevalence may range from 1 to 14% of all pregnancies, depending on the population studied and the diagnostic tests employed. Women with clinical characteristics consistent with a high risk of GDM (marked

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obesity, personal history of GDM, glycosuria or a strong family history of diabetes) should undergo plasma glucose testing. If GDM is ruled out at that initial screening, they should be retested between 24 and 28 weeks of gestation. Women of average risk should have testing undertaken at 24–28 weeks of gestation (Steven G. Gabbe, 2003). Common risk factors of GDM include nonwhite race/ethnicity, older age, obesity and prior history of DM. PCOS is a disturbed reproductive condition characterized by chronic anovulation, IR and androgen excess. Affected women have an increased risk of glucose intolerance leading to T2DM. Some studies suggest that the risk of GDM is higher among PCOS versus non-PCOS women and several studies have observed an increased prevalence of PCOS morphology and symptoms in women with prior GDM (Joan C. Lo *et al*). It is also associated with adverse pregnancy outcomes such as preeclampsia and macrosomia (Ingrid HovOdsaeter *et al*, 2015).

The major risk factors associated with GDM are age, Body Mass Index (BMI), PCOS, previous history of DM, an excessive birthweight of baby (macrosomy) and family history of diabetes (SaeedaBibi *et al*). Screening for undiagnosed DM at the first prenatal visit is recommended in women at increased risk using standard diagnostic, malformation, stillbirth, successive abortions or birthweight> 4,500 g in previous pregnancies; obesity, metabolic syndrome, age > 45 years, vascular disease; clinical symptoms of diabetes. Performance of the OGTT may already be indicated in the first trimester in some women but is mandatory between 24 and 28 gestational weeks in all pregnant women with previous non-pathological glucose metabolism. GDM is defined, if fasting venous plasma glucose exceeds 92 mg/dL or 1 h 180 mg/dL or 2 h 153 mg/dL after glucose loading (Kautzky-Willer A, 2012). In the course of pregnancy, elevated levels of reproductive hormones and other proteins having insulin-antagonistic effects lead to higher IR in peripheral tissues, followed by hyperinsulinemia. Patients with PCOS are often affected by obesity, dyslipidemia, hyperinsulinemiaand tissue-specific IR. Obesity occurs in 50% of the cases, while tissue-specific IR is observed in 20-40% of the affected patients (TadeuszIssat *et al*, 2015). Women with GDM had a history of PCOS more often than the control group of women, but regarding BMI, a history of PCOS were not shown to have a significant relationship with GDM (Kashanian M *et al*, 2008).

In a study, 220 pregnant PCOS and 594 healthy women were followed from early pregnancy. Incidences of GDM, PIH, preterm birth, twinning and fetal growth restriction were determined. The incidence of GDM was notably higher among all PCOS combined and PCOS subgroups, whether they conceived spontaneously, or via *in vitro* Fertilization and Embryo Transfer (IVF-ET) or ovarian stimulation, compared with controls. The incidence of PIH was also higher among all PCOS and the subgroup conceiving spontaneously but not for those conceiving with IVF-ET or ovarian stimulation. Lean women with PCOS had higher incidences of GDM and PIH than lean controls. PCOS women with normal OGTT had higher risk for PIH than their comparable control group. Hence PCOS is an independent risk factor for the development of GDM and PIH (Wang Y *et al*, 2013).

A retrospective cohort study of maternal/fetal outcomes in women with GDM and PCOS was compared with women with GDM alone. Multiple logistic regressions revealed that this increase persisted after controlling for BMI and parity. Women with GDM and PCOS tend to have more preterm deliveries. Logistic regression revealed that this association persisted after controlling for preterm delivery. Mothers with both disorders should be monitored more carefully and counselled regarding their increased risk of both maternal and fetal complications (Alshammari A *et al*, 2010).

In women with normal OGTT, maternal prepregnancy BMI was significantly higher in those who delivered Large for Gestational Age (LGA) new-borns than in those who gave birth to newborns below the 90th percentile, whereas there was no influence of maternal BMI on birth weight of newborns in women with GDM. There was no difference between the two groups with respect to maternal birth traumata and fetal outcome, except for plexus palsy which occurred in three GDM women with macrosomic new-borns. Strict metabolic control and surveillance in women with insulin-treated GDM seems to attenuate the risk for LGA new-borns, diabetic fetopathia and the influence of maternal BMI on fetal growth (Leipold H *et al*, 2005).

GDM affects a significant number of women each year. GDM is associated with a wide range of adverse outcomes for women and their babies. Recent observational studies have found physical activity during normal pregnancy decreases IR and therefore might help to decrease the risk of developing GDM. In a previous study four of the five included trials had small sample sizes with one large trial that recruited 855 women and babies. All five included trials had a moderate risk of bias. When comparing women receiving additional exercise interventions with those having routine antenatal care, there was no significant difference in GDM incidence, caesarean section or operative vaginal birth. None of the five included trials found significant differences in insulin sensitivity (Han S *et al*, 2012). Another study indicates that the risk of GDM is two-fold higher in women with singleton pregnancies conceived following assisted reproductive technology (ART) compared with women who conceived spontaneously. In addition, progesterone use during pregnancy was found to be an important risk factor for GDM (Ashrafi M *et al*, 2014a).

GDM affects about 5% of all pregnancies and results in an increased incidence of Caesarean sections, perinatal traumas and neonatal complications. Macrosomyis observed in new-borns from these pregnancies. In a majority of cases, diabetes regression is observed directly after pregnancy termination, however, in 15-60% of these patients, DM develops in later years of life. In the group of GDM-affected women, T2DM was diagnosed in 34 patients. The actual BMI was>25 kg/m^2 and glycaemia values in the 2nd hour of diagnostic test in the course of GDM diagnosis. The risk of DM was not enhanced in that group of women by family history of diabetes, the age of GDM onset (< 25 years of life), the week of gestation when GDM was diagnosed and the type of GDM therapy. Overweight and obesity are both risk factors of GDM, delivery of child with macrosomy features and of overt diabetes mellitus later in life (Cypryk K *et al*, 2005)

In an Iranian study, the incidence of GDM in infertile women with PCOS was compared with the women without PCOS after pregnancies resulting from either ART or spontaneous as well as to determine the risk factors of GDM in PCOS women. The most important and significant predictors for development of GDM in PCOS women are menstrual irregularity, serum triglycerides level ≥150mg/dL and the use of pregestational metformin. Pregnant Iranian women with a history of infertility and PCOS are at increased risk for developing GDM. Screening test for GDM in PCOS women with ART treatment is recommended in such patients with irregular menses and high serum triglycerides level in the early stage of pregnancy. Pregestational use of metformin can be effective in reducing the occurrence of GDM (Ashrafi M *et al*, 2014b).

GDM has a high prevalence in patients with PCOS. A consensus between early detection and classification criteria to standardize the diagnosis should be sought (Vazquez Lara Julia *et al*, 2014). In a study of infertile cases who conceived while taking metformin therapy with or without other ovulation inducing agents, who conceived without taking metformin and did not take it during pregnancy with PCOS who became pregnant were classified into two groups: group 1 included 31 cases and continued metformin during pregnancy in a dose of 1000–1500 mg daily and group 2 included 26 cases, the maternal outcome measures, such as assessment of IR, incidence of GDM, the need for insulin therapy and incidence of preeclampsia were highlighted. Fetal outcome measures include incidence of spontaneous miscarriage, preterm birth, fetal growth abnormalities, suspectedfetal asphyxia at birth, fetal anomalies and neonatal mortality. The incidence of GDM was significantly lower in cases who received metformin than those who did not receive metformin during pregnancy and spontaneous miscarriage occurred in the case in patients who continued metformin compared topatients who did not take metformin. No significant differences were observed in both groups for other outcome measures. Continuous metformin therapy throughout pregnancy in women with PCOS improves pregnancy outcomes by decreasing spontaneous miscarriage rates and prevention of GDM with its comorbidity and mortality (Azza A. Abd E Hameed *et al*, 2011). In a study, women with PCOS and GDM had more than twofold increased odds of preeclampsia and PIH. Maternal PCOS and GDM were also associated with threefold increased odds of neonatal hypoglycemia. The pregnant PCOS patients should be followed carefully for the occurrence of various pregnancy and neonatal complications including hypertension and hypoglycemia (Fatemeh Foroozanfard *et al*, 2014).

As of now GDM is diagnosed by OGTT, a rather cumbersome test for the women and health care system. In a study, fasting and 2-hr plasma glucose were measured during a 75 g OGTT in first trimester, gestational week 19 and 32 as well as fasting plasma glucose in gestational week 36. First trimester Glycosylated Hemoglobin (HbA1c) was statistically significantly associated with preeclampsia. ByWorld Health Organisation (WHO) criteria both HbA1c and GDM in first trimester were negatively associated with birth weight. First trimester HbA1c should not be used to exclude or predict GDM in women with PCOS, but it might be better to predict preeclampsia than the GDM diagnosis (Ingrid Hov Odsaeter *et al*, 2015).

There are some metabolic similarities between women with PCOS and GDM; it is still uncertain, however, to what extent coexistence GDM and PCOS affects pregnancy outcome. Ina case-control study conducted with 261 GDM women, the findings emphasized that pregnant PCOS patients should be followed carefully for the occurrence of various pregnancy and neonatal complications including hypertension and hypoglycaemia (Fatemeh Foroozanfard *et al*, 2014). Metformin is an effective insulin sensitizer treating T2DM and meta-analysis determined the effect of metformin on GDM in PCOS. This analysis examined whether metformin could reduce GDM occurrence in PCOS with a fixed effect model. The analysis demonstrated thatmetformin has no significant effect on GDM with PCOS (Zhihong Zhuo *et al*, 2014).

Infertility and GDM

A novel finding suggests that infertility, particularly from ovulation disorders and tubal blockage is associated with an increased GDM risk (Tobias DK *et al*, 2013). Women with PCOS undergoing IVF are at a substantial risk of ovarian hyperstimulation syndrome and this approach should be avoided if at all possible. If it is required these women may be suitable candidates for in vitro maturation of oocytes (IVM) so avoiding ovarian hyperstimulation. Women with PCOS are potentially at an increased risk of miscarriage and in pregnancy of they are at an increased risk of developing GDM, pregnancy-induced hypertension and pre-eclampsia. Furthermore the neonate has a significantly higher risk of admission to a NICU and a higher perinatal mortality (Hart R, 2008).

An earlier study investigated the metabolic characteristics and perinatal outcomes of GDM in women with PCOS. All GDM women were treated with medical nutrition therapy. Pre-pregnancy clinical data, fasting glucose, fasting insulin, blood lipid, homeostasis model assessment index of insulin resistance and perinatal outcomes were investigated. GDM in women with PCOS had higher pre-pregnancy BMI, higher incidence of overweight than in the non-PCOS group. Incidence of history of infertility was also significantly higher in the PCOS group than in the non-PCOS group.

A higher incidence of early pregnancy loss was found in the PCOS group than in the non-PCOS group. Significantly higher IVF-ET rate and insulin administration was also observed in the PCOS group than in the controls. No significant difference was found in the prevalence of preeclampsia, premature delivery, macrosomia, fetal death and neonatal congenital anomaly between GDM in women with and without PCOS. Compared with the controls, no significant increase in the incidence of adverse perinatal outcomes was detected in GDM in women with PCOS by appropriate management (Li G *et al*, 2010). In a Mexican study, no other between-group differences were observed in the incidence of miscarriage, preterm birth and premature rupture of membranes, preeclampsia, stillbirth, fetal malformations or small or large for gestational age newborns. Pregnant women with a history of infertility and PCOS are at increased risk for developing GDM. This risk should be considered beginning early in the second trimester for a timely intervention and to improve the maternal-fetal prognosis (Reyes-Munoz E *et al*, 2012).

CONCLUSION

PCOS is the commonest endocrine disorder in women of reproductive age occurring in approximately one in seven women. Of these women, approximately two-thirds will not ovulate on a regular basis and consequently may therefore seek treatment for ovulation induction. Pregnant women with a history of infertility and PCOS are at increased risk for developing GDM. This review article has highlighted the various researches conducted in the area of PCOS, infertility and GDM in the last decade and the contents broughtout in this article will be verymuch useful for future researchers and gynaecologists to update their knowledge and to develop a list of laboratory investigations to be carried out for all PCOS women who were diagnosed to have GDM with infertility.

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