

## First Trimester complications in pregnancy with diabetes

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### Abstract

Diabetes is the most prevalent medical condition complicating pregnancy in the world. It carries both acute and long-term health consequences for the mother and her offspring. Both preexisting (type 1 and type 2) and gestational diabetes are a high-risk state for miscarriage, stillbirths and congenital malformations in early pregnancy. Like normal pregnancy, vaginal bleeding, urinary tract infection, abdominopelvic pain, nausea, and vomiting are common presenting symptoms in early pregnancy with preexisting and gestational diabetes. Early diagnosis and appropriate management of the condition is important for improving pregnancy outcomes.

**Keywords:** First trimester complications, Pregnancy with diabetes.

### Introduction

The public health burden of diabetes mellitus has dramatically increased worldwide. Not only its prevalence rate at present, but the increase of its incidence in the near future can create a global health problem. The number of subjects with diabetes will increase from at present 415 million to 642 million by the year 2040.<sup>1</sup> In 2015, there were 199.5 million women with diabetes and 60 million of them of reproductive age (18-44 years old).<sup>1</sup>

It is estimated that about 5-20% of pregnancies in the world complicated by diabetes. It varies between different racial and socioeconomic groups. Most of the women in developing and underdeveloped countries remain undetected and many are detected during medical checkup for pregnancy. According to 7th Diabetes Atlas, hyperglycaemia in pregnancy is classified into three main types: diabetes detected prior to pregnancy or preexisting diabetes (type 1 and type 2), diabetes first detected in pregnancy and gestational diabetes mellitus (GDM) which is defined as degree of glucose intolerance with onset or first recognized during pregnancy. One in seven births is affected by GDM. According to IDF report, 20.9 million (16.2%) live births were affected by hyperglycaemia in pregnancy and an

estimated 85.1% of those cases were due to gestational diabetes, 7.4% due to other types of diabetes first detected in pregnancy and 7.5% due to diabetes detected prior to pregnancy.<sup>1</sup>

### Pathophysiology

In women with preexisting diabetes, pregnancy is associated with alteration in the regulation of glucose metabolism owing to the actions of specific placental hormones like human chorionic gonadotropin (hCG), human placental lactogen (HPL), estrogen and progesterone. As pregnancy progress these hormones result in  $\beta$ -cell hypertrophy and hyperplasia, antagonize the actions of insulin leading to the state of relatively insulin resistance and enhanced lipolysis. During the first trimester, fasting plasma glucose concentrations decline modestly in non-diabetic women reaching a lowest point at approximately 12 weeks. Post-prandial glucose levels by contrast, tend to rise whereas plasma insulin concentration remains unchanged. Effect on insulin requirements may also be influenced by pregnancy associated nausea and vomiting. From the pathophysiological point of view, the transfer of the nutrients from mother to foetus through placenta is also very important in early pregnancy. In diabetic pregnancy, due to absolute (type 1 diabetes) or relative insulin deficiency (type 2 diabetes), there is a reduced uptake and or a hyper production of nutrients by the diabetic mother and which induces hyperalimentation of embryo or the foetus. This condition in early pregnancy may induce congenital anomalies that is the main cause of foetal morbidity in diabetic pregnancy.

### First trimester complications

It is well-recognized that diabetes in pregnancy increases the risk of infant and maternal mortality and morbidity. Although complications related to diabetic pregnancy has improved considerably, still it remains higher than non-diabetic pregnancies (Table). Miscarriage, still birth and congenital malformations are the leading causes of excessive perinatal mortality related to diabetes in early pregnancy. It is now known that the vast majority of congenital foetal malformations are a consequence of abnormal embryonic development in the first 8 weeks of pregnancy. Studies also suggest that other complications of pregnancy, such as intrauterine growth restriction, preterm birth, and stillbirth, also have their origins, at

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**Table:** Maternal and foetal complications in first trimester pregnancy.

Mother	Foetus
<p><b>Gynaecological complications</b></p> <ul style="list-style-type: none"> <li>◆ Miscarriage</li> <li>◆ Ectopic pregnancy</li> <li>◆ Gestational trophoblastic disease</li> <li>◆ Abdominopelvic pain</li> <li>◆ Vaginal bleeding</li> <li>◆ Nausea and vomiting</li> <li>◆ Hyperemesis gravidarum</li> <li>◆ Urinary tract infection</li> </ul> <p><b>Metabolic (acute and chronic) complications</b></p> <ul style="list-style-type: none"> <li>◆ Hypoglycaemia</li> <li>◆ Diabetes keto acidosis (DKA)</li> <li>◆ Deterioration of underlying retinopathy and nephropathy</li> <li>◆ Increased risk of cardiovascular diseases including coronary heart disease, heart failure and stroke.</li> </ul>	<p><b>Major congenital malformations</b></p> <ul style="list-style-type: none"> <li>◆ Cardiovascular (septal defect, transposition of great vessels)</li> <li>◆ Neural tube defects (anencephaly, spina bifida)</li> <li>◆ Genitourinary (renal agenesis, duplex ureter)</li> <li>◆ Skeletal (sacral agenesis, pes equinovarus)</li> <li>◆ Facial (cleft palate or lip)</li> <li>◆ Gastrointestinal (anorectal atresia, trachea-oesophageal fistula)</li> </ul>

least in part, in very early pregnancy.

### Fetal complications

The overall risk of congenital malformations are related to maternal glycaemic status. A study has found a significant association between elevated maternal haemoglobin A1c in the first trimester of pregnancy and major congenital anomalies in infants of diabetic mothers.<sup>2</sup> This reflects the teratogenic effects of hyperglycaemia during embryogenesis. Malformations often involve the heart and central nervous system and are potentially lethal. Major congenital defects include anencephaly, spina bifida, great-vessel abnormalities and caudal regression (sacral agenesis). The rate of malformation is 2 to 4 fold higher in women with diabetes. Rates of major congenital malformations in women with type 1 diabetes range from 2.9 to 7.5 percent and 2.1 to 12.3 percent in women with type 2 diabetes.<sup>3,4</sup> Studies have also found that the rate of anomaly is 2-3 times less in women who received more aggressive preconception and first trimester management.<sup>5,6</sup> Rates of miscarriage and stillbirth are also significantly increased in comparison to non-diabetics. Pregnancy complicated by type 2 diabetes mellitus is a high-risk state, with miscarriage and stillbirth almost twice that seen in type 1 disease.

### Maternal complications

#### Gynecological complications

Like normal pregnancy vaginal bleeding, abdominopelvic pain, urinary tract infection, nausea, and vomiting are common presenting symptoms in early pregnancy. All women of reproductive age who present with abdominal or pelvic pain or with vaginal bleeding should be evaluated for possible pregnancy. Ectopic pregnancy is the leading cause of maternal death in the first trimester and accounts for 6% of all maternal deaths. Between 50% and

75% of all pregnancies are complicated by nausea and vomiting. About 25% of women experience only nausea, and 50% have both nausea and vomiting.<sup>7</sup> Vaginal bleeding in the first trimester of pregnancy is a common presenting complaint. Although it is often self-limited with no cause found, it is an important sign of serious complications, such as miscarriage, ectopic pregnancy, or gestational trophoblastic disease. Nausea and vomiting in pregnancy may also be self-limited and may occur in a normal pregnancy, but hyperemesis gravidarum should prompt the health provider to consider the possibility of gestational trophoblastic disease.

#### Metabolic (acute/chronic) complications

Poorly controlled diabetes in the first trimester is associated with hypoglycaemia and diabetic ketoacidosis (DKA). There is no evidence that episodes of maternal hypoglycaemia (which are common in insulin treated women) are harmful to foetal development but one study reported that exposure to hypoglycaemia in utero may have long term effects on offspring including macrosomia and neuropsychological defects.<sup>8</sup> DKA is less common than hypoglycaemia but this has much more serious implications, often resulting in miscarriage. Underlying retinopathy and nephropathy may worsen in early pregnancy due to vascular and volume changes. Correction of hyperglycaemia may be a precipitating factor for vascular and volume changes. Pregnancy can also increase the risk of cardiovascular diseases including coronary heart disease, heart failure and stroke.

#### Prevention of first trimester complications with preexisting diabetes

There is a clear relationship between poor diabetic control in first trimester, and it is equally established that optimal

control before conception reduces the rate of adverse events to near normal. Unfortunately, unplanned pregnancies occur in about two-thirds of women with diabetes. Lack of pre-pregnancy care facility, delay in antenatal checkup and poor glycaemic control in early pregnancy leading to a persistent excess of malformations in their infants. This may reflect on the fact that all diabetic women should be seen early in the first trimester in a joint clinic with an experienced obstetrician, diabetologist, specialist nurse and dietician. Early detection and treatment of women at high risk for these complications can improve pregnancy outcomes. But reality is, even in many developed countries this combined care concept for pregnant women is not available for majority of the population. International Diabetes Federation has given particular importance on "Life Circle" approach to prevention and care of diabetes - a continuum beginning from preconception, pregnancy, infancy and childhood to adult life in an integrated manner.

### GDM in the first trimester

Like diabetes detected prior to pregnancy or preexisting diabetes, GDM also constitutes a major health risk both for the mother and foetus. Not only for the present pregnancy but also for long-term effect of developing type 2 DM and for complications in subsequent pregnancies. The foetal programming may also affect the development of metabolic disorders for the child in adult life. Study data have shown that GDM prevalence has increased by 16% to 27% in several race/ethnicity groups during the past 20 years.<sup>9</sup> This is particularly more in Asian countries.

Based on the physiological mechanisms, screening of GDM has been advocated between 24-28 weeks. However, this has a potential to miss many cases of diabetes predating pregnancy and early onset GDM. By knowing the insulin insensitivity at the beginning of pregnancy, strategies should aim for the early normalization of the intrauterine metabolic environment at a critical period for foetal metabolic imprinting. The history of miscarriage, neonatal death and stillbirth were found higher among GDM mothers than non-GDM mothers. Unlike pre-gestational diabetes, GDM has not been clearly shown to be an independent risk factor for congenital anomalies. Malformations usually originate sometime during the first trimester of pregnancy, whereas GDM gradually develops and is least pronounced during the first and early second trimester. Studies have shown that the offspring of women with GDM are at a

higher risk for congenital malformations, and this association is more marked in overweight/obese women.<sup>10</sup>

In countries where appropriate care for obstetrical emergencies is lacking, unrecognized GDM may have particularly severe consequences for the health and well-being of the mother and their foetus. GDM is also linked directly or indirectly to haemorrhage, hypertensive disorders, obstructed labour and infection/ sepsis. All of them are among the leading global causes of maternal mortality. The need for detecting and diagnosing GDM to ensure timely treatment is therefore widely recognized as highly important.

### Summary

In summary, the present observations suggest that integrate diabetes and GDM screening and management into other maternal health interventions and services at primary healthcare level will ensure preconception counselling, early detection and better care for women with preexisting diabetes and GDM and thereby, reduced maternal and foetal loss.

### References

1. International Diabetes Federation. Diabetes Atlas. 7th edn. Brussels: International Diabetes Federation, 2015.
2. Guerin A, Nisenbaum R, Ray JG. Use of maternal GHB concentration to estimate the risk of congenital anomalies in the offspring of women with prepregnancy diabetes. *Diabetes Care*. 2007; 30:1920-5.
3. Kitzmiller JL, Wallerstein R, Correa A, Kwan S. Preconception care for women with diabetes and prevention of major congenital malformations. *Birth Defects Res A Clin Mol Teratol*. 2010; 88:791-803.
4. Al-Agha R, Firth RG, Byrne M, Murray S, Daly S, Foley M, et al. Outcome of pregnancy in type 1 diabetes mellitus (T1DMP): results from combined diabetes-obstetrical clinics in Dublin in three university teaching hospitals (1995-2006). *Ir J Med Sci*. 2012; 181:105.
5. de Valk HW, van Nieuwaal NH, Visser GH. Pregnancy outcome in type 2 diabetes mellitus: a retrospective analysis from the Netherlands. *Rev Diabet Stud*. 2006; 3:134-42.
6. Dunne F, Brydon P, Smith K, Gee H. Pregnancy in women with Type 2 diabetes: 12 years outcome data 1990-2002. *Diabet Med*. 2003; 20:734-8.
7. Badell ML, Ramin SM, Smith JA. Treatment options for nausea and vomiting during pregnancy. *Pharmacotherapy*. 2006; 26:1273-87.
8. Ter Braak EW, Evers IM, Willem Erkelens D, Visser GH. Maternal hypoglycemia during pregnancy in type 1 diabetes: maternal and fetal consequences. *Diabetes Metab Res Rev*. 2002; 18:96-105.
9. Ferrara A. Increasing prevalence of gestational diabetes mellitus. A public health perspective. *Diabetes Care*. 2007; 30: S141-6.
10. Correa A, Gilboa SM, Besser LM, Botto LD, Moore CA, Hobbs CA, et al. Diabetes mellitus and birth defects". *Am J Obstet Gynecol* 2008;199:237.e1-237.e9.