Pregnancy and Diabetes: Insulin and Beyond  
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With the evolving epidemic of obesity and metabolic syndrome, more and more women are diagnosed to have gestational diabetes mellitus (GDM) and many women with type 2 diabetes (T2DM) are pregnant. The Confidential Enquiry into Maternal and Child Health (CEMACH), reported that women with diabetes mellitus have five times the risk of stillbirth, three times the risk of neonatal death, and twice the risk of major congenital anomaly that women in general population (1). These outcomes were same for type 1 and type 2 diabetes (2).

Insulin has been traditionally the gold standard in diabetes in pregnancy because of its efficacy and the fact that it does not cross the placenta. Insulin will remain the only treatment in type 1 diabetes and no further reference will be made to type 1 diabetes in this article. ADA guidelines recommend a glucose tolerance test initially with 50 grams of glucose as a screening test and then 100 grams of glucose if screening test is positive. Normally we must have a fasting sugar test followed by 1 hour, 2 hour and 3 hour readings after giving 100 grams of glucose. The recommended cut off limits for this test are 95, 180, 155 and 145 mg% and if any of the two values are abnormal, a patient is diagnosed to have GDM. However in practice, it does not happen here in Kashmir. Most of the Gynecologist still asks for a routine fasting blood sugars and a routine urine test, and in case any one of the two points towards an abnormality, they refer the patient for Diabetes treatment. Another confounding factor here in Kashmir is that majority of the laboratories are not standardized and any abnormal report has to be read with special care and test repeated from a different laboratory. Sometimes the results are just borderline and even patients may not be ready for treatment.

Using regular human insulin and NPH insulin is the standards protocol. A 30:70 mixture is by far the easiest to use but involves some dietary time table arrangements for the patient. Two major meals 12 hours apart just after the insulin injection and small snacks in between works very well especially because women here believe that they must take small snacks throughout the day during pregnancy. This arrangement also works well when a patient has only mildly elevated blood sugars and patient needs small doses of insulin. However in case of a severe glucose abnormalities and requirement of higher doses of insulin, multiple doses are used quite frequently. One of the classical regimens we use here is bed time NPH insulin and at least three doses of regular insulin before each major meal.

Metformin is a dimethyl biguanide first described in scientific literature in 1957. This compound originates from the French lilac (Galega officinalis), a plant known for several centuries to ameliorate the symptoms of DM (3). Metformin has a diverse mechanism of action, comprising decreasing hepatic glucose output, increasing insulin sensitivity and insulin-mediated glucose use in the peripheral tissues (muscle and liver), lowering serum-free fatty acid concentration through an anti lipolytic effect and increasing intestinal glucose use. The activation of the enzyme AMP-mediated protein kinase seems to be an important mechanism by which metformin lowers the blood glucose levels. These effects of metformin make it an attractive option in diabetic pregnancy as it decreases peripheral insulin resistance, does not cause hypoglycemia nor increase insulin secretion. Patients are also likely to prefer tablets over injections. However, there has always been a reluctance to use metformin in diabetic pregnancy due to a lack of large-scale randomized studies, fear of congenital abnormalities and uncertainty over its effectiveness in this subgroup. Despite these valid concerns, there have been clinical reports of metformin use in diabetic pregnancy since 1966 (4). In those earlier studies, mainly from South Africa, the authors conclude that metformin appears to be safe for use in GDM and that the perinatal mortality rate in such women taking metformin until approximately 24 hours pre-delivery was
‘acceptable’. Metformin use has increased in women with polycystic ovarian syndrome as it has potential benefits of regulating menstrual cycles and ovulation induction. The safety and efficacy of metformin in pregnancy has come from the increasing number of such women who have gone on to conceive on metformin. A pilot study of continuing metformin use throughout pregnancy in women with polycystic ovarian syndrome showed that metformin therapy was not teratogenic and reduced the otherwise high rate of first trimester abortion seen among women not receiving this treatment (5). A systematic review and meta-analysis of eight small and non-blinded studies relating to pregnancy outcomes after first trimester exposure to metformin in women with polycystic ovarian syndrome, from 1966 to 2004, showed no evidence of increased risk of major malformations. Based on studies in Type 2 DM, the prevalence of malformations in the metformin group was 1.7%, which was within the rate for the general population. Apart from a lack of harmful effects, metformin use in the context of polycystic ovarian syndrome may have beneficial effects in pregnancy by causing a ten-fold reduction in GDM (6). The recently published MiG (Metformin versus insulin for the treatment of Gestational diabetes) study (7) has gone some way in addressing this issue. This randomized, open label trial involving 751 women with GDM (single fetus) at 20–33 weeks of pregnancy tested for non-inferiority a comparison of metformin (with supplemental insulin if needed) with insulin. Of the 363 women on metformin who completed the study, the rate of primary outcome (a composite of neonatal complications: neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5 min Apgar score below 7 or premature birth) did not differ significantly from the insulin group (32% versus 32.2% in the insulin group). Of the outcomes recorded, severe hypoglycemia (glucose level <1.6mmol/l) was less common in the metformin than in the insulin group (p= 0.008). There were no significant differences between the metformin and insulin groups in terms of maternal hypertensive complications or glycaemic control; although it has to be pointed out that supplemental insulin was used in 46.3% of women in the metformin group. The authors concluded that metformin, alone or with supplemental insulin, is an effective and safe treatment option for women with GDM. Therefore metformin may have an adjunct role to insulin which may be important in those pregnant females with marked insulin resistance and who require very large insulin doses.

First generation sulphonylureas have been avoided in pregnancy because of transplacental passage leading to fetal hyperinsulinemia, but glyburide (glibenclamide) appears to have minimal transplacental transfer. In a randomised controlled trial of glyburide versus insulin (n= 404) in gestational diabetes, there were no significant differences in perinatal or neonatal outcomes, nor maternal glycaemic control and fetal anomalies between both the groups (8). In the glyburide group, 4% of patients needed insulin therapy. In addition, glyburide was not detected in the cord serum of any of the infants in this group. Similar to metformin, a retrospective cohort study did find an increased incidence of pre-eclampsia in the glyburide group compared with the insulin group (12% vs 6%, p=0.02), but this association was not found in the prospective, randomised controlled trial. There are no direct trials comparing metformin with glyburide. This may be important as it would be useful to know whether metformin is better or worse than glyburide, as evidence until now suggests more need for supplemental insulin and transplacental transfer with metformin compared with glyburide.

References


Conflict of Interest: None

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