Decision making in hyperglycaemia seen in pregnancy

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Abstract: Delay in childbearing, family history of type 2 diabetes mellitus and obesity in childbearing years increases a possibility of glucose intolerance or overt diabetes in pregnancy which may remain unrecognised unless an oral glucose tolerance test is done. The International Association of Diabetes and Pregnancy Study Group (IADPSG, 2010) recommended the detection and diagnosis of hyperglycaemic disorders in pregnancy at two stages of pregnancy, the first stage looking for 'overt diabetes' in early pregnancy based on risk factors like age, past history of gestational diabetes and obesity and the second stage where 'gestational diabetes' at 24-28 weeks with 75 g oral glucose tolerance test. Although the one step approach with 75 g of glucose offers operational convenience in diagnosing gestational diabetes, there are concerns raised by the National Institute of Health in the recent consensus statement, supporting the two step approach (50-g, 1-hour loading test screening 100-g, 3-hour oral glucose tolerance test) as the recommended approach for detecting gestational diabetes. Medical nutrition therapy (MNT) with well-designed meal plan and appropriate exercise achieves normoglycemia without inducing ketonemia and weight loss in most pregnant women with glucose intolerance. Rapidly acting insulin analogues, such as insulin lispro and aspart are safe in pregnancy and improve postprandial glycemic control in women with pre-gestational diabetes. The long acting analogues (Insulin detemir and glargine) though proven to be safe in pregnancy, do not confer added advantage if normoglycemia is achieved with intermediate insulin (NPH). Current evidence indicates the safe use of glyburide and metformin in the management of Type 2 diabetes and gestational diabetes as other options. However, it is prudent to communicate to the women that there is no data available on the long-term health of the offspring and the safety of these oral hypoglycemic drugs are limited to the prenatal period.

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Diagnosis of hyperglycemic disorders in pregnancy

The fundamental weakness in categorisation of what is termed 'gestational diabetes mellitus' (GDM) lies in women not being aware of prevailing diabetes when they become pregnant (pre-existing diabetes mellitus (DM), both Type 1 (T1DM) and Type 2 (T2DM). The diabetogenic action is mounted by pregnancy hormones such as corticotrophin releasing hormone, placental lactogen and growth hormone coupled with other factors inherently seen in pregnancy such as accumulation of fat. Weight gain out of proportion to normal invariably contributes to increasing insulin resistance with advancing gestational age even in the absence of T1DM and T2DM. When the conventional definition of GDM of 'abnormal glucose intolerance in pregnancy' is applied it would clearly include a proportion of patients who have undetected pre-existing DM. However, attempts at newer categorisations has not met uniform consensus. The International Association of Diabetes and Pregnancy Study Group (IADPSG, 2010) proposed a novel categorizstion of 'overt and gestational'. Overt diabetes is when the fasting blood sugar >7 mmol/L and HbA1c >6.5 % or a random blood sugar >11 mmol/L.[1] These criteria would be meaningfully applied when screening for GDM is done in early booking especially in the first trimester based on 'risk criteria".[1,2] Delaying screening to conventionally recommended glucose testing using the 75 g glucose at 24-28 weeks would effectively miss a proportion of GDM who would benefit from therapeutic manipulation to maintain a euglycemic state avoiding the often dreaded complication of macrosomia, perinatal mortality and intrapartum complications.

'Gestational diabetes' is diagnosed when FBS >5.1 mmol/L but is less than 7.0 mmol/L at any gestational age. The traditional 75 g oral glucose load

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at 24-28 weeks should have at least one abnormal value i.e. FBS <5.1,7.0 mmol/L, 1 hour >10mmol/L and 2 hour >8.5 mmol/L.[1]

At the moment, this one step approach with 75 g glucose as proposed by IADPSG is recommended by WHO and has been adopted by countries outside the United States. The American College of Obstetrician and Gynaecologist (ACOG) however still recommends the two step approach (50-g, 1-hour loading test screening and 100-g 3-hour oral glucose tolerance test) as they are of the opinion that the one step approach will result in increase in healthcare costs with no evidence of clinically significant benefits on maternal and fetal outcome.[3]

As the debate continues, the National Institute of Health proposed the NIH Consensus Development Conference in March 2013 to reach a uniform opinion. The NIH panel concluded that the two step approach would be the recommended diagnostic method for gestational diabetes due to concerns related to one step approach such as increased frequency in diagnosis (from 5 to 15%), patient anxiety, increased clinic visits, intensive monitoring, caesarean delivery and additional health costs. The conclusions were largely based on the fact that there is still paucity of evidence that treatment of mild gestational diabetes improves maternal and fetal outcomes.[4] By far the most important epidemiological study on pregnancy outcome was 'The Hyperglycemia Adverse Perinatal Outcome (HAPO) Study'. At the same time of the HAPO study, two randomised controlled trials that used the same glucose threshold values as in HAPO study compared active treatment with the standard obstetric care for women with mild GDM. Both the trials demonstrated improved outcomes such as large for gestational age, or birth weight >90th percentile and preeclampsia in the treated group and the results are complementary to the HAPO study.[5,6,7] Despite these encouraging results, the composite outcome of neonatal morbidity and caesarean delivery has not consistently improved with treatment and there is paucity of evidence of the long-term outcomes for mothers and their off springs with regards to childhood obesity and maternal metabolic complications.

The NIH panel identified priority research with randomised trials that would evaluate the diagnostic threshold of adverse outcomes, comparing the outcomes of the two diagnostic approaches (one step versus two step) their cost effective analysis, patients' preferences and their psychological consequences of the diagnosis (medicalisation of pregnancy) that would change future decisions on diagnostic techniques.

Pre- pregnancy care (PPC): A shared responsibility

Women with T1DM and T2DM should have preconception planning to achieve and sustain glycemic control that minimises the risks of fetal malformation and spontaneous miscarriage. In a report from California Diabetes and Research project, it was stated that congenital malformations are more frequent in T2DM compared to T1DM due to unawareness of the risk and lack of preconception care.[8] This emphasises the need for the primary care providers to identify women with risk factors for diabetes such as obesity, acanthosis nigricans, polycystic ovarian syndrome, hypertension, parents and siblings with T2DM and promote contraceptive measures so as achieve optimum glycaemic control.[9] In a systematic review and meta-analysis by Wahabi *et al* (2012), the effectiveness and safety of pre-pregnancy care in improving the rate of congenital malformations and perinatal mortality in women with pre-gestational diabetes was evaluated. It was reported that preconception care reduces the incidence of congenital malformations and lowers the glycosylated haemoglobin A1C (HbAIC) by 1.92%. This meta-analysis revealed that only 34-38 % of eligible women actually utilise the pre-pregnancy care services. The authors highlighted the importance of routine integration of PPC services in reproductive age, prevention of unplanned pregnancies and the need for further research as priority to identify the methods that will encourage the diabetic mothers to utilise the PPC services.[10]

Pregnancy Care

The ultimate goal of optimal care in the management of diabetes (pregestational and GDM) is to achieve euglycemia throughout pregnancy and this is best attained through a multidisciplinary team approach including diabetic physician, dietician, nurse educator and family members.[11, 12]

Medical Nutrition Therapy (MNT)

Medical nutrition therapy is a programmed therapeutic strategy that should be adopted in combination with exercise and pharmacological intervention.. Attention to maternal weight gain is relevant in management through a well-designed meal plan and appropriate exercise. Although evidence is sparse by way of well-designed studies, it is prudent to focus on medical nutrition therapy as fundamental to the management of GDM. In both overt and gestational DM, MNT should be instituted as the sole strategy or in combination with pharmacological therapy. Clearly where DM is detected early or the patient has pre-existing DM, MNT alone may be insufficient for optimum glucose control. T1DM and poorly controlled T2DM are categorised as being at higher risk of requiring pharmacological therapy from the outset especially when they are also overweight. Islet cell plasticity promotes increased insulin production in normal pregnancies especially when pregnancy hormones contribute to increased insulin resistance in the second half of pregnancy. This physiological response of islet cells of the pancreas is inadequate in overt DM and hence both MNT and pharmacological treatment are mandated to achieve desirable blood glucose level.

The meal plan should be such that adequate calories are provided for sufficient energy through pregnancy based on gestational age, body constitution, occupation and category of GDM. A typical meal plan would constitute frequent well-spaced meals constituting two main ones (lunch and early dinner) interspersed with snacks at mid-morning, mid-afternoon, and supper prior to retiring at night. The goal is to ensure that meals provide sufficient calories through the day and need to be synchronised with either oral hypoglycemics and/or insulin therapy.

The American Diabetic Association emphasises the need to provide adequate calories so as to promote optimal weight gain and promote fetal growth. Women should be discouraged to skip meals and avoid heavy meals so as to prevent sustained and elevated postprandial blood glucose which appears to contribute to macrosomia. Normal pregnancies would require a minimum of 1800 kcal/day. The role of a dietician is to advise on what constitutes a balanced diet and how much calories are required, individualising the requirements based on body type and activity.[13, 14]

A guide on calories requirements is shown in Table 1, based on glucose goals, weight gain and nutrient intake.

Table 1: Calorie needs of Gestational diabetes mellitus[14]

Body Weight	Kcal/kg/day
Ideal body weight	30
Overweight	22-25
Morbidly obese	12-14 (present body weight)
Underweight	40

As it is vital to synchronise pharmacological therapy to MNT the meal plan should be well-spaced throughout the day with appropriate individual meal calorie manipulation of the total calories needs. Again it is imperative for patients to be educated to be aware that the carbohydrate content has a direct bearing on postprandial glucose best demonstrated by periodic assessment of capillary blood sugar using a self-monitored glucometer. Although in women with ideal body weight, adopting a formula of 50% carbohydrate with the rest of the calories being derived equally from protein and fat is feasible, some therapeutic manipulation would be needed in those who are beyond the ideal body weight. A changed formula of complex carbohydrate of 40%, protein 20% and 40% fat (with no more than 7 % coming from saturated fat) should be advised. The quality of

food should be aligned to the likes of the patient and her cultural background to improve adherence to meal plan. Although caloric restriction is not adopted in MNT in the normally built patient, the Dietary Reference Intakes advocate such a strategy in those who weigh beyond 30 kg/m2.[14]

Pharmacological therapy for diabetes in pregnancy

Insulin therapy has been in vogue as to complement MNT in the management of diabetes for over 30 years. Since the discovery of insulin by Banting and Best in 1922, rapid technological advances have led to the development of several types of pharmacological agents.[15] Apart from insulin, insulin analogues and certain groups of oral hypoglycaemics are being increasingly used in medical practice.

Insulin therapy

Human insulin and insulin analogues

The earlier insulin preparations were derived from porcine and bovine sources that had variable and unpredictable efficacy due to impurities that were immunogenic. Adverse effects such as hypoglycemia unawareness are attributed to these insulin antibodies. The recombinant human insulin emerged in 1986 with the substitution of alanine for threonine on the porcine insulin sequence. However 80% of diabetics treated with subcutaneous insulin still demonstrated insulin antibodies that can significantly alter its pharmacokinetics. The hypothetical explanation is that the insulin antibodies can serve as carrier and prolong the effects of insulin or decrease its efficacy by neutralising its actions. It is identified that the insulin binding sites of the antibodies vary among the individuals and therefore the pharmacodynamics. This resulted in exploration of exogenous agents that can closely mimic the physiological peripheral response of insulin by slightly modifying its amino acid sequence.[16] Thus insulin analogues were introduced with insulin lispro in 1996. Currently, only recombinant human insulin and insulin analogues preparations are available and the beef and pork insulin preparations were phased out in 2003 and in 2005.[17]

Rationale of insulin therapy in pregnancy

Maternal glucose crosses the placenta by facilitated diffusion. Maternal insulin does not cross the placenta unless it is bound to IgG antibody. Menon *et al* (1990), hypothesised that antibody bound insulin in the fetus is an important determinant of fetal outcome such as macrosomia that is independent of maternal glycemic control.[18] This led to the need for an exogenous insulin therapy that is of low immunogenicity which would minimise placental transport of insulin. However, relevance of these insulin antibodies to neonatal outcome is still unclear. Balsells *et al* (1997) in his study demonstrated that maternal insulin antibody levels did not influence the fetal outcome.[19] This was further supported by Mc Cance *et al* (2008) that the level of insulin aspart and human insulin specific antibodies were low throughout pregnancy and there was no correlation between birth weight and cord blood human insulin ($p=0.1590$). Insulin aspart antibodies were undetectable in the cord blood of all participants. This study provided new information on the use of insulin analogues in pregnancy.[20]

Pharmacokinetics and evidence for efficacy and safety of insulin in pregnancy

To understand endogenous insulin physiology, the concept of basal and bolus insulin need to be defined. Basal insulin is background insulin that is released by the beta cells of pancreas and is present throughout the day and bolus dose is the insulin that is released in response to glucose from the meals (postprandial peaks). Simulating this mechanism of release of endogenous insulin is achieved by both basal (intermediate or long acting insulin) and bolus dose (short or rapid acting insulin) either as multiple dose injections or continuous subcutaneous pumps. Essentially, 40-50% of daily total dose of insulin replaced should be the basal insulin to

cover for overnight and between meals and the other 50-60% is in the form of bolus dose of insulin so as to cover glucose rises due to carbohydrate that is consumed and postprandial hyperglycemia.[21]

Types of insulin

There are currently four types of insulin preparations depending on the time of onset and duration of action which include short acting insulin, rapid acting insulin analogues, intermediate acting insulin and long acting insulin analogues (Table 2). For achieving near-normoglycemia, these insulin preparations should have similar pharmacokinetics as endogenous insulin. This refers to their action which results in rapid rise in insulin after the administration, short duration of peak insulin levels, rapid decline of insulinemia for short acting insulin and even insulinemia without peaks or glycemic excursions in (blunting effect) intermediate acting insulin.[22] The optimum glycemic control is therefore achieved by combination of long acting and rapid acting insulin as basal–bolus dosing mimicking normal physiological insulin patterns.

Regular human insulin

Regular human insulin is short acting insulin that is the least immunogenic. The specific problems related to regular insulin is its slow onset of activity that results in inadequate control of postprandial hyperglycemia, long duration of action and potential for late postprandial hypoglycaemia.[23]

Rapid acting insulin analogues

The rapid acting insulin analogues are insulin lispro, aspart and gluisine. The insulin analogues are produced by recombinant DNA technology. The lispro is prepared from *E.coli* and it differs from human insulin in the substitution of two amino acids in the beta chains. The amino acid lysine is substituted at position 28 and proline at position 29. The aspart has the yeast *Saccharomyces cerevisiae* to replace the proline by aspartic acid in position 28. The glulisine has a double substitution that replaces aspargine by lysine at position 3 and lysine by glutamic acid at position 29. The effects of these modifications in the beta chains results in insulin analogues that form monomers which are rapidly absorbed upon administration and quick onset of action.[24]

Regular human vs rapid acting insulin analogues: evidence in pregnancy

The rapidly acting insulin analogues are comparable to regular insulin with respect to their immunogenic properties. The onset of action of rapid acting insulin analogues is faster with earlier peak concentration and brief duration of action that prevents postprandial hyperglycemia and late onset hypoglycaemia.[24] However only lispro and aspart have been investigated in pregnancy and have demonstrated considerable safety profiles with no risk of teratogenicity.[25] In a study by Jovanovic *et al* (1999) comparing the effects of lispro with regular insulin in gestational diabetes, lispro was undetected in the cord blood, indicating no placental transfer. The mean fasting postprandial levels and HbA1c were the same in both groups with lispro demonstrating lower hypoglycemic episodes.[26] In a randomised control trial in pre-gestational TIDM, insulin aspart was found to be superior to isophane insulin (NPH) in reducing the risk of postprandial glycemic excursions and delayed the postprandial hypoglycaemia.[27] In an observation study on safety of insulin lispro in TIDM, T2DM and gestational diabetes, which analysed 635 pregnancies over a period of 7 years, it was concluded that patient satisfaction was considerable with insulin lispro ($P<0.05$) with no difference in maternal or fetal outcomes, whether patients used regular insulin ($n=138$) or insulin lispro ($n=75$), and with lower antepartum HbA1c with insulin lispro ($p<0.05$).[28]

Intermediate acting Insulin

Neutral Protamine Hagedorn (NPH) still remains the basal insulin of choice during pregnancy due to

its flexibility in adjusting the dosage in response to calorie intake. Nocturnal hypoglycaemia is of concern with NPH due to its peak action occurring 5-7 hours of the dose that is less likely to reduce even with the consumption of bedtime snack. This is addressed by shifting the pre-dinner NPH insulin to bed that delays the peak action to early morning thereby avoiding the overnight hypoglycaemia.[29]

Long acting insulin analogues

The long acting insulin analogues are glargine and detemir. In glargine, glycine is substituted by aspargine at position 21 and two arginine molecules are added at the carboxyl end. In detemir, there is elimination of threonine and substitution by myristic acid by acylation. This process of amino acid modification shifts the pH to neutral and this delays absorption, self-aggregation and therefore prolongs the duration of action.[23]

Neutral Protamine Hagedorn (NPH) insulin vs long acting insulin analogues: evidence in pregnancy

In a retrospective study by Callesen *et al* (2013), the glycemic control and pregnancy outcome was compared between insulin detemir and glargine in TIDM. It was concluded that both the long acting insulin analogues are safe in pregnancy with similar glycemic control and pregnancy outcomes except that glargine was associated with low incidence of macrosomia.[30] The insulin and insulin like growth factor receptor- 1- binding properties, mitogenic properties of glargine were found to be increased in comparison to other insulin analogues in a study by Kurtzhals *et al* (2000). This raises the concern of its safety in pregnancy.[31] In a recent meta-analysis by Lepercq *et al* in 2012, exposure of long acting insulin analogue glargine, in all trimesters of pregnancies demonstrated no adverse maternal and fetal outcome compared with NPH insulin. However, it was noted that the number of women treated with glargine in the first trimester is small to provide conclusions on its safety with respect to teratogenicity.[32] Regarding insulin detemir, a recent randomised, controlled non-inferiority trial compared the efficacy and safety of insulin detemir versus NPH in pregnant women with TIDM. The primary outcome, suggested non-inferiority of insulin detemir to NPH with respect to HBA1c at 36 gestational week.[33] Following this study results, detemir received Food and Drug Aadministration (FDA, USA) approval as category B drug from Category C. However, at the moment, with the available evidence, it is not prudent to initiate glargine in pregnancy unless more data is obtained from large randomised controlled trials and although the evidence for detemir is favourable, there is no compelling evidence for the routine use of this drug in pregnancy.[34]

Table 2: Types of insulin and insulin analogous and their pharmacokinetic properties[24, 25]

Name and Type of Insulin	Onset of Action	Peak Effect	Duration of Action
Short Acting Insulin Regular Insulin	60 minutes	2-4 hours	6 hours
Rapid Acting Insulin Analogues (Bolus) Insulin lispro Insulin aspart	15 minutes	60 minutes	2 hours
Intermediate Insulin NPH (Basal)	2 hours	4-6 hours	8 hours
Long Acting Insulin Analogues (Basal) Insulin glargine Insulin detemir	2 hours	No peak effect for insulin glargine Insulin detemir is 3-9 hours	12 hours
Recommended Intervals of Dosing **Regular Insulin**: 60 minutes before each meal, **Rapid Acting Analogues**: At the start of each meal, **Intermediate Insulin** : Every 8 hours, **Long Acting Analogues**: Every 12 hours			

Insulin requirements in pregnancy and dosage

In a study by Patterson *et al.* (2010), the total insulin requirements through the gestation is noted to vary with an early rise between 3 and 7 weeks, declining between 7 and 15 weeks and followed by a rise in remainder of pregnancy. This reflects pregnancy related alteration in glucose metabolism and nausea and vomiting in early pregnancy.[35]

The average insulin requirement in pregnancy is calculated as shown below:

Woman's weight kilograms x k = total insulin requirements: i.e k = units of insulin/kg body weight.[36]

1-18 weeks	18-26weeks	26-36weeks	36-40weeks
0.7unit/kg wt	0.8unit/kg wt	0.9unit/kg wt	1 unit/kg wt

An excess weight gain in pregnancy mandates more insulin and doses of 1.5-2.0units/kg to overcome the insulin resistance due to pregnancy and obesity. About 2/3 of the total dose is given in the morning (that includes: 33% rapid-acting, 66% intermediate-acting) and 1/3 in the evening with 50% as rapid-acting insulin before dinner and 50% as intermediate insulin before bed.[37]

Calculating total 24h hours insulin requirement and dose distribution in a pregnant women at 37 weeks gestation with a body weight of 70 kg

1. First calculate her 24-hour total dose: 0.9 x 70 = ~54 units' total insulin per day.
2. Give 2/3 total dose (36 units) in the AM and 1/3 (18 units) in the PM

Type of Insulin	Pre-Breakfast	Pre-Dinner	Before Bed
Rapid acting Insulin-Lispro or Aspart	12 Units	8 units	
Intermediate acting insulin -NPH	24 units		10 units
NPH before bed: Usually requires doses more than 50% to prevent dawn or early morning hyperglycemia			

Table 3: Clinical Practice Points

1. Rapidly acting analogues, insulin lispro and aspart are safe in pregnancy and improve postprandial glycemic control in women with pre-gestational diabetes.
2. When adequate glycemic control is achieved with human insulin it is not necessary to convert to rapid acting analogues in view of cost-benefit
3. Recent studies indicate that long acting analogues has no adverse fetal effects and they effectively reduce the incidence of hypoglycemic episodes.
4. Both the drugs (Insulin detemir and glargine) are proved to be safe in pregnancy. However, with lack of definitive fetal beneficial outcome there is no indication for routine use of long acting analogues.
5. In women with gestational diabetes and T2DM, with little concern for hypoglycemic episodes, there is no evidence to routinely initiate long acting analogues for glycemic control.

Oral hypoglycemic agents

The pathophysiology of T2DM and gestational diabetes is due to inadequate insulin secretion and resistance and therefore the rationale of treating with oral hypoglycemic agents that stimulate the release of insulin from the functional cell of the pancreas, increases the insulin sensitivity of peripheral tissues, and as act as insulin secretogogues.[38] Although traditionally insulin is considered the gold standard in the management due to its efficacy in achieving euglycemia, it may still prove to be inconvenient owing to its cost and invasiveness of the therapy.[39]

Evidence for the use of oral hypoglycemic agents in pregnancy

The second generation sulfonylurea, glyburide has extensive evidence in pregnancy. In an *in vitro* study with single-cotyledon placental model, glyburide was found to only marginally cross the placenta. This was followed by a landmark randomised trial by Langer *et al* (2000) which observed that that there was no frequency of macrosomia or neonatal hypoglycaemia or maternal adverse effects with the use of glyburide in pregnancy.

The study demonstrated that there was no detectable glyburide level in the umbilical cord despite reaching therapeutic concentrations of the drug in the maternal blood. However, on close observation it was identified that the study failed to achieve normoglycmia and the cord samples were inadequate to evaluate its safety.[40]

Moving forward, few retrospective trials on glyburide in pregnancy have emerged with the facts that glyburide still fails in 20% of clinical population and the need for subsequent insulin therapy and the rate of neonatal hypoglycaemia and hyperbilirubinemia is increased when compared to insulin.[41] Recent studies on pharmacokinetics of glyburide, suggest that the peak action is between 2 to 4 hours following the administration of the drug. The fact that peak in glucose occurs at 90 minutes after taking a meal suggests that glyburide should be administered at least 60 minutes prior to a meal to prevent postprandial glucose excursions.[42,43] The questions that remain elusive are whether glyburide affects the long term wellbeing of the newborn and the future progression of gestational diabetes to metabolic syndrome. Until then it is pragmatic to counsel women on the limited information available albeit the fact that glyburide is an alternative choice in women with gestational diabetes, who fail diet therapy and unable to comply with insulin therapy.

The other oral hypoglycemic agent that is demonstrated to be effective is metformin especially in conditions such as polycystic ovarian syndrome, where it reduces incidence of pregnancy loss and onset of gestational diabetes by improving the insulin sensitivity. The benefits of using metformin in pregnancy are further substantiated in the randomised controlled trial by Rowen *et al* (2008) which is the 'Metformin in gestational diabetes trial (MiG trial)'. It was stated that metformin is not associated with increased perinatal complications as compared with insulin and the women preferred metformin to insulin treatment.[44]

In a follow up study of the exposed children at 2 years in the " The offspring follow up trial" (TOFU trial) it was observed that metformin exposed infants had more subcutaneous fat and less visceral fat that may translate to increased insulin sensitivity pattern of growth in future.[45] Regarding thiazolidinediones and meglitinides in pregnancy ,there is paucity of data with regards to their safety.[38]

Intrapartum management

The target range of intrapartum glycemic control in TIDM, T2DM and gestational diabetes is 3.9-6.1 mmol/l. This level is determined from the neonatal outcomes studies of various observational studies in TIDM women and is the recommendation by the American College of Obstetrician and Gynaecologist.[13]

Insulin and glucose requirements during labour

Insulin requirements vary in patients with overt DM (T1DM, T2DM) and gestational diabetes. In women with T1DM there is no endogenous insulin whereas women T2DM and gestational diabetes have sufficient endogenous basal insulin that decreases the complications of diabetic ketoacidosis. Thus women with T1DM will require basal insulin infusion to maintain euglycemia during latent phase of spontaneous and induced labour.[46]

Labour in general has a glucose lowering effect. In the latent phase of labour, the maternal metabolic demands are not increased and excess glucose is not mandatory. As active labour ensues, the glucose requirement is similar to sustained and vigorous exercise with rapid depletion of hepatic glycogen stores. It is identified that there is a need for an eight fold increase in glucose substrates to meet this demand of glucose which is achieved by glucose infusion at the rate of 2.5mg/kg/mt to maintain maternal euglycemia.[47]

What's new in glucose monitoring intrapartum?

The standard approach is monitoring of capillary blood glucose concentration at every two to four hours in latent phase and every one to two hours in active phase,

and with insulin infusion, it is every hour monitoring. The continuous glucose monitoring system (CGMS) is a technology that measures the interstitial glucose every 1 to 10 minutes for a maximum of 3 to 6 days and provides a comprehensive assessment of glycemic control than the intermittent monitoring. The reliability, specificity and accuracy of CGMS intrapartum was looked at in two pilot studies, in which the authors concluded that there were no episodes of neonatal hypoglycemia or respiratory distress syndrome and all women reported feeling secure checking their glucose concentrations in real time. CGMS provides information trends rather than at point data. There is a delay of about 10 minutes when compared to capillary blood sugar determination and patient worn devices may create unnecessary anxiety should there be 'hypo- and hyperglycemia'. The device is expensive and may be inconvenient as it has to be worn for 3-7 days depending on the make of the device. However preliminary studies in pregnancy shows that physician monitored CGMS improved hypoglycaemia awareness. We need more large prospective trials to determine its feasibility and cost-effectiveness before incorporating in the protocol of intrapartum glycemic monitoring.[48, 49]

Insulin and infusion in labour

Insulin is not required in majority of women with GDM controlled with diet. In the event of antepartum insulin, only a minority will require insulin in labour. In an audit of routine practice of insulin and glucose infusion in labour in pre-gestational and gestational diabetes, Barett *et al* (2009) identified that neonatal hypoglycaemia is common with blood sugar levels between 4-8 mmol/l. The authors suggested that with relaxed capillary blood glucose targets, only 2 % of women on diet and 3.5% of women on insulin in gestational diabetes require insulin therapy in labour. This calls for considering more conservative approach over the aggressive regimens in these women.[50] Sliding scale insulin in considered in women with pre-gestational diabetes in labour and delivery by elective caesarean section. Women admitted for induction should have their normal insulin doses the night before, once admitted they need short acting insulin to cover the meals and intravenous sliding scale once labour established. In a comparative study of constant intravenous insulin infusion with continuous subcutaneous insulin infusion pump (CSIIP) intrapartum in 28 women, Feldberg *et al* (1988) concluded that CSIIP was superior in achieving and maintaining intrapartum optimal metabolic control, reducing the incidence of acute fetal distress, caesarean section and neonatal hypoglycaemia.[51] Epidural analgesia for pain relief in labour has significant advantages as it decreases the maternal endogenous catecholamine release and indirectly increases the placental blood flow, reduces the maternal lactic acid and hence fetal acidosis.[52]

Anaesthesia implications: Perioperative considerations

The consequence of surgery and anaesthesia in a diabetic patient stimulates a neuroendocrine stress mechanism with the production of counter regulatory hormones that can result in hyperglycemia and ketosis. Hence the goal of perioperative management is preventing hyperglycemia, hypoglycemia, prevention of ketosis and maintenance of adequate hydration and electrolyte balance.[47] For caesarean section, regional anaesthesia is indicted compared to general and there is no specific preference for spinal over the epidural anaesthesia. Either spinal or epidural anaesthesia may be suitable in diabetic pregnancies.[52] A dextrose free fluid such as normal saline is used for hydration prior to induction of anaesthesia as large glucose bolus reduces the umbilical cord pH and neonatal hypoglycaemia. Sanjay Datta and his colleagues demonstrated that spinal anaesthesia is a safe technique for caesarean delivery in diabetics, with particular caution to avoid hypotension and correction of acute hydration with dextrose free solutions. If the surgery is prolonged, the glucose should be monitored as hyperglycemia during surgery is associated with risk of postoperative wound infection and neonatal hypoglycaemia.[53] There are additional

risks associated with long standing diabetes related to autonomic neuropathy such as orthostatic hypotension, painless MI, reduced response to medication-atropine and propranolol, resting tachycardia, decreased cough reflex threshold, increased incidence of obstructive sleep apnoea and gastroparesis. A thorough preoperative assessment with history, examination and investigations is paramount to evaluate for end organ damage.[52]

Future directions

The research in diabetes is rapidly evolving with new modalities in the diagnosis, monitoring and treatment. There are undoubted benefits of the insulin analogues and oral hypoglycaemic agents in pregnancy as evidenced so far. With the outset of risk involved in clinical trials in pregnancy, it can perhaps be unrealistic to expect more information on the safety profiles of these drugs. At the moment, clinicians have to rely on their knowledge on the current evidence available on the diagnostic approaches and pharmacodynamics and the outcomes of randomised trials that will guide them on the decision making process in pregnancy. There are few studies that demonstrate that portal insulin delivery and inhaled insulin delivery have dynamics closer to endogenous insulin and are expected to make the management of diabetes much easier. However, we need to synthesise high evidence on safety and efficacy of these routes of delivery in pregnant women.

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