

Insulin Analogue Therapy in Pregnancy with Diabetes



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Abstract

Recent advances confirm that, the poor maternal glycemic control during pregnancy is associated with risk of maternal and fetal complications. Avoiding hyperglycemia improves pregnancy outcome. With the incidence of both type 1 and type 2 diabetes is increasing, it becomes further important to establish optimal therapies and medications for the treatment to contain the complications. The conventional insulin especially regular human insulin because of its pharmacokinetic properties makes aggressive control of glycemic parameters in diabetic pregnant far from reach. Tightening the glycemic control with available conventional insulins was associated with increase in the risk of major hypoglycemia, with other potential adverse maternal outcomes viz coma, seizures, and maternal death. Compared with regular human insulin (RHI), rapid acting analogues with the fast onset and relatively shorter duration of action match the changed physiological requirement more closely in pregnancy. These insulins benefit pregnancy complicated by diabetes by providing better control of postprandial hyperglycemia with less hypoglycemia. Even macrosomia, the most significant neonatal complications associated with GDM that has got direct correlation with increasing post prandial hyperglycemia has been best addressed by rapid acting insulin analogues. Currently there is no regulatory approval for the use of long acting and premix analogue insulins in pregnancy. However they are being used by many practitioners and also clinical trials are underway for their use in diabetes in pregnancy. The modern insulins along with modern delivery devices which offer painless and accurate dosing have made insulin therapy more convenient and acceptable.

The occurrence of congenital malformations continues to be the leading cause of mortality and serious morbidity in infants of mothers with type 1 and type 2 diabetes in spite of advancement in understanding pregnancy metabolism and treatment. The perinatal morbidity also remains relatively high in women who develop glucose intolerance of any degree with onset or first recognition during pregnancy, gestational diabetes mellitus. Thus the fetus of pre-gestational diabetic women, gestational diabetic women, or any woman with abnormal glucose tolerance in pregnancy is at risk of developing either congenital malformation or morbidity in the form of macrosomia and other metabolic disorders. Clinical trials have established that preconceptional care and attaining good glycemic control during all the trimesters of pregnancy have resulted in striking reduction in maternal and fetal morbidity. Thus it has become imperative, to obtain optimum glycemic control and at the same time to avoid hypoglycemia during pregnancy. Perinatal outcome data indicates that the best level to maintain fasting plasma glucose [FPG] is ≤ 90 mg/dl and 2 hr post prandial glucose [PPG] level ≤ 120 mg/dl¹. Maintaining plasma glucose ≤ 120 mg at 1 hour is gaining importance¹.

The first step in the management of glucose intolerance during pregnancy is to advise Medical Nutrition therapy [MNT]. Pregnant women who fail to respond to MNT are recommended insulin. When insulin therapy is initiated, the goal is to prevent both post meal hyperglycemia and pre meal hypoglycemia. The existing human insulin falls short of maintaining ideal glucose

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level during pregnancy due to its pharmacokinetic action profile. They have a high tendency for self association to form hexamers, the predominant form present in the insulin vials. The dissociation rate of human insulin (hexamer) through dimer and into monomeric form is slow at the subcutaneous site of injection and consequently its absorption is also retarded because insulin is absorbed only in the monomeric form. Therefore the pre prandial administration of human insulin is not able to control the peak post prandial plasma glucose and at the same time the slow absorption results in inappropriate hyperinsulinemia before the next meal resulting in pre prandial hypoglycemia. Thus the conventional human insulin is not able to mimic the

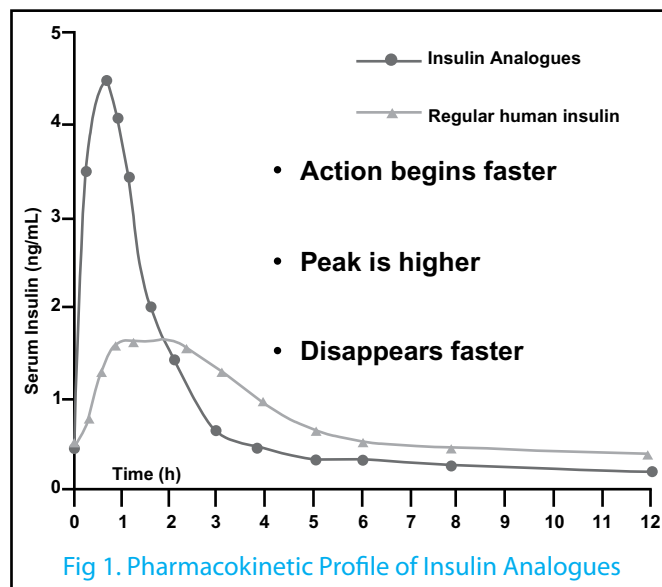


Fig 1. Pharmacokinetic Profile of Insulin Analogues

Table 1 : Receptor binding and metabolic and mitogenic potency of insulin analogues

	Insulin receptor affinity	Metabolic potency	IGF-I receptor affinity	Insulin receptor off-rate (%)	Mitogenic potency (Saos/B10 cells)
Human insulin	100	100	100	100	100
Insulin lispro	84 ± 6	82 ± 3	156 ± 16	100 ± 11	66 ± 10
Insulin aspart	92 ± 6	101 ± 2	81 ± 9	81 ± 8	58 ± 22
Insulin glargine	86	60 ± 3	641 ± 51	152 ± 13	783 ± 13
Insulin detemir	~18 - 46	~27	16 ± 1	204 ± 9	~11

Data are means ± SD. Adapted from Kurtzhals et al. (27)

physiological insulin kinetics resulting in unacceptable glycemic profile. In this regard, the rapid acting insulin analogues are likely to overcome the drawbacks of the conventional insulin due to their unique pharmacokinetic action profile. After subcutaneous administration of the rapid acting analogue, the serum insulin concentration peaks two times higher, in less than one half of the time compared with an equal dose of Regular Human Insulin [RHI]². This results in the differences in the pharmacokinetic and dynamic profile of rapid acting insulin analogues compared with RHI. The action begins quicker, peaks faster and disappears faster (Fig 1).

Rapid-acting Insulin Analogues

Insulin aspart : It was approved for clinical use in 1999. Insulin aspart, is obtained by a structural modification where in proline in B28 position is replaced with negatively charged aspartic acid which offers an ultra-short acting pharmacokinetic property to it. It has a very rapid onset of action, peaking from 31 to 70 min after subcutaneous injection, and duration of action being 2 to 4 h³, whereas RHI peaks after 2-4 hours and action profile lasts for 6-8 hours. It has a faster and more effective glucose lowering action, and thus superior control of postprandial hyperglycemia. The prandial glucose was lower by 30% at 1 hr and 53% at 2 hr with analogues compared to RHI⁴. Interprandial and nocturnal hypoglycaemia are less common with insulin analogue than with RHI.

Insulin Aspart efficacy and safety in pregnancy has been proved in several clinical studies across the world including India^{5, 6}. In a parallel-group, randomized, controlled, multi-centre study in 322 pregnant women with diabetes, treatment with insulin aspart was associated with a 52% lower rate of major nocturnal hypoglycemia and similar overall glycemic control to RHI^{7, 8}. Pregnancy outcomes like live births, fetal losses and congenital malformations were also significantly improved in those who received insulin aspart. They had less pre-term deliveries compared to women receiving RHI (p=0.05). Insulin aspart does not cross the placenta and there was no increase in cross-reacting insulin antibodies. The occurrence of perinatal complications was also comparable between insulin aspart and RHI. Furthermore, in women with insulin-requiring GDM, insulin aspart was more effective than RHI in reducing the PPG (9). With insulin aspart treatment in pregnant women with diabetes, there was no increase in cross-reacting insulin antibodies and no evidence of transfer of insulin aspart across the placenta was noted^{7,8}. Insulin aspart is approved for continuous subcutaneous infusion and offers a valuable treatment option during pregnancy. There have been no insulin-associated maternal or fetal complications and no evidence that insulin aspart is teratogenic¹⁰. Insulin aspart has been approved by both US FDA and European Union for use during pregnancy.

Insulin lispro: In this insulin, aminoacids Lysine and Proline respectively at β chain 29th and 28th position are swapped. The pharmacokinetic profile of lispro is similar to that of aspart. Anecdotal studies of lispro in pregnancy have shown better efficacy and safety than RHI; however use of insulin lispro in pre GDM is still a concern though the teratogenicity has not been conclusively established¹¹. Lispro is categorized B in the USFDA list.

In general, rapid acting insulin analogues therapy during pregnancy in patients with type 1 and type 2 DM resulted in normalization of glycemic control and had no detectable adverse effects on maternal or fetal outcomes^{12, 13, 14}. There is no evidence that the use of rapid acting insulin analogues during pregnancy results in an increased rate of congenital malformations or they are mutagenic¹⁵. Analogues appear to be safe alternative to RHI in the treatment of diabetes during pregnancy^{7, 16, 17}. It is important to note that the insulin profiles with the two rapid-acting insulin analogues are very similar and there are unlikely to be any significant clinical differences but, the broader insulin peak observed with aspart may convey advantage, which include greater mealtime flexibility. If the insulin peak is broader with aspart and its effects sustained, it is reasonable to assume that a delay in eating of up to 15 minutes would have no adverse effect on blood glucose. The narrow peak associated with insulin lispro may infer less flexibility and an increased need to eat immediately following insulin injection. It is also likely that the broader insulin peak seen with aspart conveys greater pre-prandial glucose control, with the effects of aspart being sustained from one meal to the next^{18, 19}.

Control of Post Prandial Hyperglycemia During Pregnancy

The most significant neonatal complications associated with GDM is macrosomia²⁰. The risk of macrosomia increases with increasing post prandial hyperglycemia^{21, 22, 23}. Studies have documented that the peak glucose concentration occurs 1 hr after eating¹⁹. RHI is not able to make a significant impact in lowering the PPG control⁹. Rapid acting analogues achieve a higher peak insulin concentration in less time and with a short duration of action than RHI when given 5 minutes before a meal⁹. Improved fetal outcome and less risk of neonatal hypoglycemia, macrosomia and caesarian delivery occurred in GDM managed by controlling PPG concentration²³

Control of Fasting Hyperglycemia During Pregnancy

Insulin glargine has several potential advantages in the management of pregnancies complicated by type 1 diabetes. Nocturnal hypoglycemia may be a significant clinical problem in women attempting to maintain the stringent glycemic targets

recommended for diabetic pregnancies²⁴. Because nocturnal hypoglycemia is less common with bedtime insulin glargine – versus bedtime NPH²⁵, it may offer clear advantages in the clinical setting but due to ongoing safety concerns, insulin glargine in pregnancy needs caution²⁶. Among the long-acting insulin analogues, glargine had an elevated IGF-1 receptor affinity (6.5 times more) and mitogenic potency compared to RHI, while detemir had more than five-fold lower IGF-1 receptor affinity and mitogenic potency (Table 1). Insulin detemir could probably be safer in pregnancy with respect to development or progression of maternal retinopathy²⁷. Till the safety of insulin analogues is established biphasic insulin aspart (BIAsp) can be given with dinner. By administering BIAsp in the morning as well as in the evening, both fasting and post prandial hyperglycemia can be controlled safely and effectively¹⁷.

Insulin Delivery Devices

Modern insulin delivery devices like S Pen which use 31G needles make the injections accurate, discreet and painless. The acceptability for insulin therapy is increasing amongst patients. These devices have made the insulin administration convenient and resulted in maintaining maternal glucose at optimal levels (28).

The story of glucose control does not end with insulin, but monitoring control is also of paramount importance. It should include frequent monitoring of blood glucose levels with an aim to achieve normoglycaemia without significant hypoglycaemia. In all these cases fasting and postprandial blood glucose values should be measured regularly and Self-monitoring of blood glucose (SMBG) should be emphasized. Careful monitoring and dose adjustments are required towards the end of pregnancy, labour and after delivery as during this time insulin requirements undergo several changes.

Conclusion

All pregnancies are precious and diabetic pregnancy is even more precious. Abnormality of glucose tolerance is detrimental to the health of both mother and her offspring. Due to the direct linkage between maternal glycemic control and fetal morbidity and mortality, treatment of diabetes in pregnant women becomes further more crucial. Early detection of diabetes is key to favorable outcomes, thus emphasizing the need for screening all pregnant women for glucose intolerance. Any abnormality of glucose tolerance has to be managed aggressively for better maternal and perinatal outcomes. Insulin therapy is the mainstay of glucose control. The development of insulin analogues has made the achievement of maternal normoglycemia more attainable, and has increased the convenience of insulin therapy. Compared to RHI, Insulin Aspart has shown better outcomes in diabetic pregnancies. This along with simpler and convenient modern insulin delivery devices like Flexpen, NovoPen3 has revolutionized therapy in GDM. Most importantly there is a greater acceptance and compliance in adhering to therapy, resulting in a better fetal outcome.

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