

## TREATMENT OF DIABETES DURING PREGNANCY

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*Key words: diabetes mellitus, pregnancy, hypoglycemic agents, insulin, insulin analogs*

### SUMMARY

*Diabetes complicates up to 14% of pregnancies, and with the rising prevalence of obesity and diabetes in younger population groups it may become an even greater problem. Poor metabolic regulation is a precipitating factor for unfavorable pregnancy outcome or fetal macrosomia. The possible treatment options for women with diabetes are reviewed, with special reference to novel treatments.*

### INTRODUCTION

According to the American Diabetes Association (ADA), gestational diabetes is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (1). This definition also includes previously unrecognized diabetes or diabetes beginning concomitantly with the pregnancy. A portion of pregnant women were also previously known diabetics. In contrast, the World Health Organization (WHO) does not distinguish between gestational and previously known diabetes (2). Gestational diabetes prevalence is estimated at about 1%-14% of all pregnancies, depending on the population and the type of test used (3).

Women at high risk of gestational diabetes are those with marked obesity, personal history of gestational diabetes mellitus, glycosuria, or a strong family history of diabetes. Women at low risk of gestational diabetes are those at the age below 25, normal body weight before pregnancy, without family history of diabetes or personal history of glucose intolerance, and without poor outcome in previous pregnancies. All other women are at medium risk. The ADA Clinical Practice Recommendations advise testing for all high risk women in early gestation and again between 24<sup>th</sup> and 28<sup>th</sup> week of gestation, and for those at medium risk only between 24<sup>th</sup> and 28<sup>th</sup> week of gestation. For low risk women no testing is suggested (3).

Women with gestational diabetes have an increased incidence of maternal and fetal complications (4). The frequency of congenital malformations and perinatal mortality is increased in both types of diabetes (5,6). The most common fetal complication is macrosomia (7). Poor glycemic regulation is a precipitating factor for complications or macrosomia (8-10). Currently, all efforts are made to achieve the best possible regulation in all women with gestational diabetes, and the ADA Clinical Practice Recommendations from 2004 suggest the following glycemic values: <5.8 mmol/l fasting, <8.6 mmol/l 1-hour postprandial or <7.2 mmol/l 2-hour postprandial (3).

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### *Oral hypoglycemic agents*

Sulphonylureas are known to cross the placental barrier depending on their molecular mass. Three hours after absorption tolbutamide attains a cumulative transplacental transfer of 21.5%, chlorpropamide 11% and glibenclamide (glyburide) only 3.9% (11). Anecdotal data on fetal malformations after exposure to sulphonylureas have been reported (12,13), but the metabolic disorder *per se* has not been considered as a possible teratogenic factor (14). Subsequent studies could not confirm an increased number of malformations or higher fetal morbidity in women treated with glibenclamide/metformin combination (15). The first large prospective study was the one conducted by Ravina. In this study, women were consecutively treated with diet, metformin, sulphonylurea and insulin if the desired control could not thus be achieved. The total number of pregnancies was 600, of which 102 were treated with metformin and 67 with glibenclamide. No increase in teratogenesis or neonatal hypoglycemia was observed, and perinatal mortality was similar in all groups (16). A recent, randomized and controlled study confirmed that glibenclamide and insulin were equally successful in achieving a satisfactory glycemic control, and pregnancy outcomes were similar (17). Out of 400 women, 200 were treated with glibenclamide and 200 with insulin, glibenclamide being started after the 11<sup>th</sup> week of gestation (after organogenesis had been completed).

All these studies raised debate about glibenclamide as a possible alternative treatment in gestational diabetes. Nevertheless, it has not yet been accepted as a standard treatment for fear from malformations or postpartal neonatal hypoglycemia.

Metformin has recently been used in the treatment of polycystic ovary syndrome (POS). There are reports on pregnancies conceived during metformin therapy for POS. These reports reveal lower incidence of spontaneous abortions, absence of teratogenesis, and normal children's growth and development for up to 6 months *post partum* (18,19). On the other hand, a Danish study (50 women treated with metformin, 68 with sulphonylurea and 42 with insulin) showed a

significantly higher incidence of preeclampsia in the metformin group, with higher perinatal mortality in the last trimester (20).

Acarbose has not been systematically analyzed in the treatment of pregnant women with diabetes. There is a report from Mexico on six women in whom glycemic regulation was achieved with acarbose, and the pregnancies were completed by deliveries of healthy babies (21). The potentially unfavorable (although not proven) influence of acarbose on pregnancy could be due to the increased amount of starch in the bowels of the women treated with acarbose. The bacterial breakdown of starch leads to the accumulation of butyrate, which could increase the prostaglandin E secretion, with negative consequences on pregnancy (22).

PPAR agonists (thiazolidindiones) are novel insulin sensitizing agents. There are no data on their possible influence on pregnancy. *In vitro*, they accelerate biochemical and morphologic differentiation of human trophoblast (23). As they are also used in the treatment of POS (24), it is to be expected that pregnancies will occur in the women treated with thiazolidindiones.

### *Insulin*

Insulin is traditionally the first choice treatment for diabetes during pregnancy, as it is the most natural agent for hyperglycemia that cannot be treated with diet therapy alone. It does not cross the placenta, except as an insulin-antibody complex (in women who have developed insulin antibodies) (25,26). Insulin can cause fetal macrosomia, which is a risk factor for fetal death, probably due to increased oxygen requirements (27-29). Fetal macrosomia has been observed in women with high insulin in cord blood or amniotic fluid (30). High fetal insulin levels are the consequence of maternal hyperglycemia rather than insulin treatment, as glucose crosses placenta and causes fetal hyperinsulinemia. In women with gestational diabetes insulin antibody formation has been observed as well as insulin-antibody passage to fetal circulation, but without adverse effect on pregnancy compared to control groups (31). It is uncertain whether the complexes are metabolically active.

The purpose of insulin treatment is substitution of its endogenous secretion. Endogenous secretion is a complex process which is reliant on meals, physical

activity and activity of other hormones. In fasting state there is a steady insulin secretion (basal secretion), and healthy beta cells can increase their secretion substantially after meals or stimulation with glucose or other secretagogues. Imitation of such endogenous secretion is a demanding task requiring good collaboration between the patient and medical staff (32). Conventional intensified insulin treatment consists of one or two doses of intermediate-acting insulin and three (preprandial) doses of short-acting insulin.

The best substitution method is the use of insulin pumps (33,34). Pump delivers a steady infusion rate for basal needs, which can be modified for different requirements during different periods of the day, and patient determines the dose and the time of bolus delivery. Disadvantage is the necessity of special education of both patient and medical staff as well as high pump cost.

### Insulin analogs

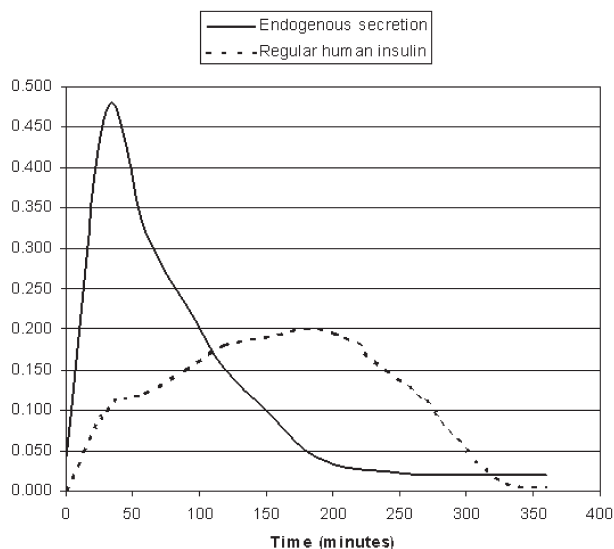
In order to achieve the near-normal glycemia, a subcutaneous applicator of exogenous insulin should have similar pharmacokinetic properties as insulin secreted from the pancreas in healthy individuals. This means rapid rise in insulin concentration after the application, short duration of peak insulin concentrations, and rapid decline in insulinemia after the application for short-acting insulins and an even insulinemia without peaks for long-acting insulins. Purified porcine or human insulin preparations do not meet these requirements (35,36) (Fig. 1). Therefore, attempts have been made to remodel insulin molecule with the purpose of changing its pharmacokinetic properties into more favorable ones. By changing the primary amino acid sequence, changes in the tertiary structure can be achieved, which could influence the association of molecules as well as the duration of insulin-receptor binding, which can also lead to an increased mitogenic action of the insulin analog (37).

In the lispro insulin molecule, the sequence of 28<sup>th</sup> and 29<sup>th</sup> molecule is inverted (proline-lysine into lysine-proline). This results in the modification of the conformation of the insulin molecule, which becomes more similar to IGF-1 molecule and the affinity to form dimers and hexamers decreases (38). The pharmacokinetics of lispro insulin is more similar to the insulin response in healthy individuals (39). The rise in insulin

concentration is faster than with regular insulin, and peak concentrations are higher (40,41). Insulin lispro can better manage postprandial hyperglycemia than regular human insulin without increasing the risk of hypoglycemia (42-49). It can lead to moderate glycemic control improvement (48,50,51) and decrease in nocturnal hypoglycemia (46), the latter being the major advantage.

Insulin aspart has the 28<sup>th</sup> amino acid in beta chain (proline) replaced with aspartate, which changes the polarity and leads to faster dissociation after the application. The pharmacokinetic and pharmacodynamic profile of insulin aspart resembles that of lispro insulin, although minor differences exist (52). The affinity for IGF-1 receptor and mitogenicity of insulin aspart are similar to human insulin (37).

Figure 1. Pharmacokinetics of endogenous insulin secretion and exogenous human insulin.



In clinical studies, insulin aspart given immediately before the meal was more successful than regular insulin 30 minutes prior to meal in reducing postprandial hyperglycemia (53-56) and number of nocturnal hypoglycemic episodes (55,56).

The pharmacokinetic properties of regular human insulin and rapid-acting analogs are shown in Table 1.

The third rapid-acting analog, glulisine, has lysine at B3 position and glutamine at B29 position. The mitogenic and metabolic properties are similar to human insulin (57). The pharmacokinetic and pharmacodynamic properties of glulisine are comparable to lispro insulin (58).

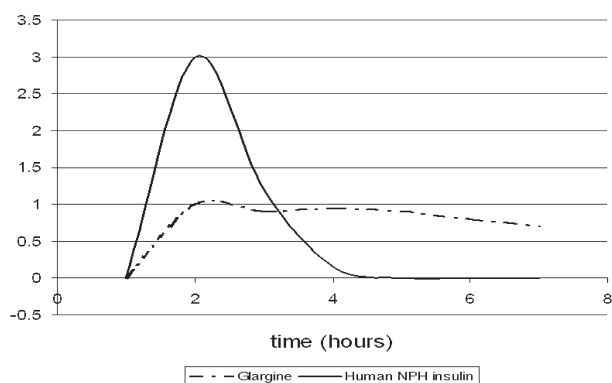
Table 1. **Pharmacokinetic properties of regular human insulin and rapid-acting analogs**

Type of insulin	Onset of action	Peak plasma values	Duration of action
Regular human insulin	30-60 minutes	1-2 hours	4-6 hours
Insulin lispro	15-30 minutes	1-2 hours	2-4 hours
Insulin aspart	10-20 minutes	1-2 hours	2-4 hours

Human insulin preparations with intermediate duration of action are aimed to cover the basal insulin requirements (fasting and between meals). There are two basic types: NPH (Neutral-Protamine-Hagedorn) and zinc-insulin. These long-acting insulin preparations are associated with two major problems. Both are suspensions and thorough mixing prior to use is critical, which bears the possibility of mistake (59). Also, there are significant inter- and intraindividual differences in the absorption rates and bioavailability (60-63). Neither of the preparations can cover the basal insulin requirements for the entire 24-hour period (64,65). In the multiple injection therapy regimen with regular insulin, the prolonged action of regular insulin also covers the basal insulin needs between meals during the day. A special problem is the unfavorable pharmacokinetic profile of NPH insulin. The peak action of NPH insulin occurs 5-7 hours after the application (66). If the evening dose is given before bed time (around 10.00 p.m.), the peak action will occur between 3.00 and 5.00 a.m., when the need of insulin is lowest, bearing a high risk of hypoglycemia. In patients with type 1 treated with multiple injection therapy, about 50% of all hypoglycemic episodes occur during the night. Between 5.00 and 8.00 a.m., insulin sensitivity and insulin concentration decrease, which leads to the dawn phenomenon (67,68). Glargine is a human insulin analog with prolonged action. The molecule of glargine has the isoelectric point of pH 6.7, in contrast to pH 5.4 of human insulin. A modification has been made on the C-terminal end of B-chain, where arginine molecules have been added, and glycine at A-21 position has been substituted with arginine. The pH of the preparation is 4.0, at which glargine is completely soluble. At a more neutral pH of the tissue microprecipitation takes place, which delays resorption. Resorption is also additionally delayed by a small amount of zinc added (69,70).

Glargine has the same affinity for insulin receptor as human insulin, whereas the affinity for IGF-1 receptor is 3- to 14-fold greater, however, without known clinical significance (37). After subcutaneous application glargine reaches its maximum activity after 4-5 hours, which then remains even without pronounced peaks (71) (Fig. 2). The main advantage of glargine used in intensified therapy is the lower incidence of severe and nocturnal hypoglycemia (72-76).

Figure 2. **Pharmacokinetics of human NPH insulin and insulin glargine.**



Another long-acting insulin analog is detemir, which is currently in phase III clinical trials. In the detemir molecule the threonine at B30 position is removed, and myristoyl fatty acid is acylated to lysine at B29. Its prolonged action is believed to be due to a combination of hexamer formation and reversible albumin binding. About 98% of detemir in plasma are bound to albumin, and only the free fraction can activate insulin receptor. Detemir is soluble at neutral pH, and subcutaneous depot remains in soluble state, which makes the resorption surface larger and diminishes resorption variability (77). Detemir has a lower receptor affinity than human insulin, and even lower IGF-1 affinity and mitogenic potential (37). It has been demonstrated that detemir needs to be given in four-fold equimolar NPH insulin doses to achieve the same hypoglycemic potential (78). No interactions with other albumin-bound drugs have been observed (79). Detemir has lower intraindividual pharmacokinetic variability than NPH insulin (80). Detemir also has a relatively stronger effect on the liver than on peripheral tissues (81,82).

The pharmacokinetic properties of long-acting human insulin and long-acting analogs are shown in Table 2.

Table 2. Pharmacokinetic properties of long-acting human insulin and long-acting analogs

Insulin type	Onset of action	Peak plasma values	Duration of action
Ultratard HM Novo	4 hours	8-24 hours	18-28 hours
Glargine	4-5 hours	–	> 24 hours
Detemir	4-6 hours	–	20 hours

Lispro is the only insulin analog that has been adequately studied in pregnancy.

One of the first studies is from 1999, with 42 pregnant women randomized to receive lispro or regular insulin. With lispro insulin the areas under the curve (AUC) for glucose, insulin and C-peptide were smaller, and the frequency of hypoglycemia was lower. HbA1c, and fasting and postprandial blood glucose revealed similar regulation in both groups. Neither lispro nor regular insulin was found in the cord blood, and the level of insulin antibodies was equal in both groups. No fetal malformations or neonatal abnormalities were observed in either group (83).

Neither did another, retrospective study (138 pregnancies treated with regular insulin and 75 treated with lispro) show any unfavorable pregnancy outcomes or fetal malformations with lispro insulin. HbA1c in the lispro group was significantly lower, and patients were more satisfied with the treatment (84). The second retrospective study in 33 pregnant patients treated with lispro and 27 treated with regular insulin did not show any higher risk of malformations or unusual pregnancy outcomes in patients treated with lispro either (85). The third retrospective study summarized pregnancy outcomes for 78 pregnancies treated with lispro insulin. The frequency of abortion, congenital malformations, perinatal mortality, glycemic control and retinopathy progression was similar to other large studies in pregnant women with diabetes (86).

Persson *et al.* report on a multicentric, randomized open study of metabolic regulation in 33 pregnant type 1 patients (17 treated with regular and 16 with lispro insulin). In the lispro group the frequency of severe hypoglycemia was lower, but there were significantly

more biochemical hypoglycemic episodes. HbA1c values did not significantly differ between the two groups, and so did not other complications, the method of delivery or fetal complications (87).

One of the significant points when initiating lispro treatment in pregnancy was the rate of retinopathy progression, as there have been some observations of its possible acceleration (88). Two studies were so designed and conducted as to investigate the occurrence and progression of retinopathy in lispro treated pregnancies, and found neither accelerated progression nor more frequent retinopathy development (89,90).

Insulin aspart was tested in only one study in women with gestational diabetes. It was compared with regular insulin or diet treatment, in its capacity to lower postprandial glycemia. Regular insulin was given 30 minutes and lispro 5 minutes prior to meal. The AUC for glucose did not significantly differ between the regular insulin and diet group, whereas with aspart it was significantly smaller (91).

There is only one report on the use of glargine in pregnancy. The patient with type 1 had frequent, severe nocturnal hypoglycemic episodes and her NPH was substituted for glargine. The frequency of hypoglycemia could be reduced by maintaining a satisfactory metabolic control. The patient had previously been free from retinopathy and it did not occur during pregnancy. Pregnancy was terminated by normal vaginal delivery of a healthy baby, which was not macrosomic, and apart from transient (<48 hour tube feeding) hypoglycemia had no adverse postpartal events (92).

## CONCLUSION

The aim of diabetes treatment in pregnancy is normoglycemia. Fetal malformations and macrosomia as well as other related complications can be avoided by maintaining glycemia within the normal values. If basic treatment with diet and exercise does not result in the desired level of glycemic control, the treatment of choice is human insulin, applied as intensified treatment.

With the rising prevalence of obesity and type 2 diabetes in younger population groups, more pregnancies are to be expected in women with undiscovered diabetes (but already with poor metabolic regulation) as well as in women treated with

various peroral hypoglycemic agents. Therefore intensive counseling in younger women with type 2 diabetes regarding preconception regulation is of utmost importance in order to achieve good regulation with agents compatible with pregnancy. Also, all efforts should be made to diagnose as many cases of type 2 diabetes as possible prior to pregnancy in the population of young women who are at risk of developing diabetes (especially those who are obese). The data available do not suggest an increased risk of

malformations in patients treated with glibenclamide or in those treated with metformin in early pregnancy, however, its use is not recommended.

Rapid-acting insulin analogs are a possible alternative to regular human insulin. The clinical data available as well as animal and *in vitro* models provide no evidence for possible adverse effects on either the fetus or pregnancy outcome.

Data on long-acting analogs are very sparse, so these analogs cannot be recommended in pregnancy for the time being.

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