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2012

Insulin analogues in the treatment of diabetes in pregnancy

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Análogos de insulina no tratamento do diabetes gestacional

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SUMMARY

Pregnancy affects both maternal and fetal metabolism, and even in non-diabetic women, it exerts a diabetogenic effect. Among pregnant women, 2% to 14% develop gestational diabetes. Pregnancy can also occur in women with preexisting diabetes, which may predispose the fetus to many alterations in organogenesis, restrict growth, and the mother, to some diabetes-related complications, such as retinopathy and nephropathy, or to acceleration of the course of these complications, if they are already present. Women with gestational diabetes generally start their treatment with diet and lifestyle changes; when these changes are not enough for optimal glycemic control, insulin therapy must then be considered. Women with type 2 diabetes using oral hypoglycemic agents are advised to change to insulin therapy. Those with preexisting type 1 diabetes should start intensive glycemic control. As basal insulin analogues have frequently been used off-label in pregnant women, there is a need to evaluate their safety and efficacy. The aim of this review is to report the use of both short- and long-acting insulin analogues during pregnancy and to enable clinicians, obstetricians, and endocrinologists to choose the best insulin treatment for their patients. Arq Bras Endocrinol Metab. 2012;56(7):405-14

SUMÁRIO

A gravidez afeta tanto o metabolismo materno quanto o fetal e, mesmo em mulheres não diabéticas, apresenta um efeito diabetogênico. Entre as mulheres grávidas, 2% a 14% desenvolvem o diabetes gestacional. A gravidez pode ocorrer também em mulheres já diabéticas, o que pode predispor o feto a muitas alterações na organogênese, restrição de crescimento e a mãe a algumas complicações relacionadas ao diabetes, tais como retinopatia e nefropatia, ou acelerar o curso dessas complicações se já estiverem presentes. Pacientes com diabetes gestacional geralmente iniciam seu tratamento com dieta e mudanças no estilo de vida; porém, quando essas medidas falham em atingir um controle glicêmico adequado, a insulinoterapia deve ser considerada. Pacientes com diabetes tipo 2 em uso de hipoglicemiantes orais são aconselhadas a iniciar o uso de insulina. Pacientes com diabetes tipo 1 preexistente devem iniciar um controle glicêmico estrito. Em função do fato de os análogos basais de insulina estarem sendo utilizados muito frequentemente *off-label* em pacientes grávidas, faz-se necessário avaliar sua segurança e eficácia nessa condição. O objetivo desta revisão é avaliar o uso de tais análogos, tanto de ação curta como prolongada, durante a gravidez, para possibilitar médicos clínicos, obstetras e endocrinologistas escolher o melhor regime terapêutico para suas pacientes. Arq Bras Endocrinol Metab. 2012;56(7):405-14

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INTRODUCTION

Normal pregnancy is a condition characterized by a series of complex hormonal adaptations that occur to ensure that sufficient glucose is available to meet the nutritional requirements of the growing fetus without causing maternal hypoglycemia (1). As normal pregnancy progresses, there is an increase in insulin resistance that may result in gestational diabetes (2). Pregnancy can also occur in women with preexisting diabetes. A significant increase in preexisting diabetes in pregnant women has been observed in the USA between 1999 and 2005, rising from 10% to 21% (3). Pregestational diabetes, both type 1 and type 2, can cause alterations in fertilization, throughout pregnancy, and even after delivery. It can predispose the fetus to many alterations in organogenesis, restrict its growth, and predispose the mother to some diabetes-related complications, such as retinopathy and nephropathy, or accelerate the course of these complications, if they are already present. Gestational diabetes generally leads to fetal growth alterations (2).

Pregnant women with diabetes present increased risk of complications, and their offspring, of neonatal morbidity and mortality. Many population-based studies have explored the impact of diabetes on pregnancy outcomes in women with pregestational (types 1 and 2) and gestational diabetes (4). Poor pregnancy outcomes, such as increased risks of congenital malformations, preterm delivery, fetal and neonatal loss, pre-eclampsia, Cesarean section and maternal morbidity and mortality, occur in one in every four women with pregestational diabetes (5,6). Recently, the incidence of type 2 diabetes has increased in parallel with the growing prevalence of obesity, with more cases of type 2 diabetes being diagnosed in pregnant women, even in adolescents and young adults (3). Pregnancy outcomes in women with type 1 and type 2 diabetes are still poor, and they are similar in both types of diabetes; some studies have even found the same or worse rates of adverse outcomes in women with type 2 diabetes (6). The presence of gestational diabetes can result in birth injuries, shoulder dystocia, macrosomia, and neonatal hypoglycemia, as well as increased perinatal morbidity and mortality (7).

The aim of this review is to review the literature on the current use of both short- and long-acting insulin analogues during pregnancy, regarding their safety and efficacy, and to enable clinicians, obstetricians, and endocrinologists to choose the best insulin treatment protocol to achieve and maintain normal blood glucose levels in all diabetic pregnancies.

ADVERSE OUTCOMES IN PREGNANCIES OF WOMEN WITH DIABETES

Hyperglycemia, a hallmark of diabetes, is a major cause of maternal and fetal morbidity, since excessive blood glucose can alter maternal metabolism in many ways, and can have teratogenic effects in the fetus, which frequently complicate diabetic pregnancies (1,2). The most common adverse outcomes found in pregnancies of women with diabetes are fetal and neonatal losses; stillbirths; a great variety of congenital abnormalities and malformations; premature delivery (delivery occurring before 37 weeks of gestation); macrosomia (defined as a birth weight above 4 kg and/or > 90th percentile weight for gestational age), which is associated with several obstetric complications; hypertension; pre-eclampsia; hypoglycemia; and higher rates of maternal and fetal mortality (4,5).

Pregnancy loss is significantly higher among women with diabetes compared with the non-diabetic population (4). Recently, a population-based cohort study conducted in the UK by Casson and cols. has shown that women with type 1 diabetes have greater risk of late fetal loss, presenting a four- to five-fold increase in perinatal death, and a four- to six-fold increase in the rate of stillbirths (8) compared with the general population. Neonatal mortality is also about 15-fold higher among infants of diabetic mothers when compared with the general population (4). The increased risk of congenital abnormalities found in diabetic mothers seems to be associated with poor metabolic control during organogenesis, which occurs in the first trimester of pregnancy, probably due to the negative impact the hyperglycemic milieu has in the growing fetus (9). Congenital malformations of all types have an incidence four to ten times greater in pregnant women with diabetes (7). The major congenital malformations found among offspring of women with diabetes are bone malformations, congenital heart disease, and neural tube, cleft lip and palate-associated anomalies (6,10). These major congenital abnormalities are important contributory factors for the high mortality rates found in infants of women with diabetes (8). Preterm delivery is four to five times more frequent among mothers with diabetes (4). Preterm infants, born to women with any type of diabetes, have much greater risk of presenting a wide

range of complications, such as intrauterine growth restriction, low birth weight, respiratory distress syndrome, hypoglycemia, hypocalcemia, polycythemia, intrauterine death, hyperbilirubinemia, several types of malformations, hypertrophic cardiomyopathy, and asphyxia, compared with those born to women without diabetes (4).

Glucose is transported freely across the placenta by facilitated diffusion; in the presence of maternal hyperglycemia, large amounts of glucose reach the fetus, leading to fetal hyperinsulinemia, which causes fetal overgrowth and/or macrosomia. Besides hyperglycemia, high levels of other metabolic fuels, such as some aminoacids and free fatty acids, might as well increase fetal insulin secretion and lead to macrosomia (10). The rates of macrosomia are 3.5-4.5 times greater among infants of women with pregestational diabetes than those found in infants born to non-diabetic mothers (11). Macrosomia is associated with several obstetric complications, such as higher rates of Cesarean section, shoulder dystocia, chorioamnionitis, severe perineal lacerations, and postpartum hemorrhage (11). Morbidity and mortality rates are also higher among pregnant women with diabetes. Rates of pre-eclampsia (12.7%), Cesarean sections (44.3%), and maternal mortality (0.6%) found among women with type 1 diabetes are considerably greater than in the general population. Hypertension and postpartum hemorrhage are more likely to be found in pregnancies complicated by diabetes (12). Pregnant women with type 1 diabetes present a death rate 109 times greater than the general population, and 3.4 times greater than in non-pregnant type 1 diabetic women (13).

Changes in glucose disposal and insulin kinetics seen in pregnancy have special importance for women with pregestational diabetes because hypoglycemia, many times of severe intensity, can generally occur in early pregnancy, a period when insulin requirements may decrease, possibly because of nausea and vomiting, compared with prepregnancy and the second half of pregnancy; it is a dangerous condition that can have important after-effects, both to the mother and to the fetus (14).

TREATMENT OF DIABETES IN PREGNANCY

The treatment of diabetes in pregnancy requires lifestyle modifications, medical nutrition therapy and physical activities, along with pharmacological treatment that should promote normal or near-normal glycemic levels and adequate weight gain. During the second and third trimesters of pregnancy, there is a steady increase in insulin resistance. This results in fasting and postprandial hyperglycemia, hyperlipidemia, and hyperaminoacidemia. These metabolic disturbances are the targets of therapeutic interventions performed in diabetic pregnancies in order to obtain good metabolic control (2).

INSULIN THERAPY DURING PREGNANCY

Insulin is the treatment of choice for any type of diabetes during pregnancy; most of insulin preparations used today have been shown to be safe and promote good glycemic control during pregnancy. If the patient has pre-existing type 2 diabetes being treated with oral hypoglycemic agents, she is advised to discontinue these medications and start using insulin, as soon as a possible pregnancy is diagnosed; if the pregnancy is planned she should be advised to start using insulin even before she becomes pregnant (15).

Before the discovery of insulin in 1922, the outcomes of less than 100 pregnancies were reported in women with diabetes. The rates of mortality both for the mothers and infants were very high, being greater than 90% for infants and 30% for the mothers, respectively (16).

Lower infant mortality rates started to be noted after 1980, when the importance of more strict control of maternal plasma glucose levels started to be stressed, and self-monitoring of blood glucose and the evaluation of hemoglobin A1C became available. After then, near-normal blood glucose levels became possible to be achieved and maintained throughout pregnancies of women with diabetes; consequently, ever since, perinatal mortality rates have reached levels observed in the general non-diabetic population (16).

The targets for glycemic control during pregnancy are pre-breakfast plasma glucose levels of 60-90 mg/dL (3.3-5.0 mmol/L), preprandial levels of 60-105 mg/dL (3.3-5.8 mmol/L), one-hour postprandial levels < 140 mg/dL (7.8 mmol/L), two-hour postprandial levels < 120 mg/dL (6.7 mmol/L), and levels between 2 am to 4 am > 60 mg/dL (3.3 mmol/L); these targets for one-hour postprandial levels might be even lower, preferably below 120 mg/dL (6.66 mmol/L) in order to avoid macrosomia. All these levels should be obtained without the occurrence of hypoglycemia (15,16).

The treatment of any type of diabetes in pregnancy should be done with the use of non-immunogenic

insulins, that is not able to cross the placenta unless bound to IgG antibodies. In contrast, facilitated diffusion helps glucose cross the placenta; therefore, maternal high blood glucose levels would stimulate the fetal pancreas to produce high amounts of insulin and, consequently, cause macrosomia (17).

The transfer of insulin bound to immunoglobulin through the placenta has been associated with fetal macrosomia in mothers with near-normal glycemic levels during gestation (18). However, Jovanovic and cols. have found that only very strict blood glucose control, reached by one-hour postprandial glucose levels lower than 120 mg/dL (6.66 mmol/L), but not lower insulin antibody levels, were correlated with lower fetal weight and lower rates of macrosomia. This means that adequate one-hour postprandial glucose levels, but not insulin antibodies against exogenous insulin, can influence infant birth weight (18).

Insulin requirements rise during pregnancy because of progressive increase in insulin resistance generally associated with weight gain and decreasing physical activity. Insulin requirements grow progressively in a rate of 0.7, 0.8, and 0.9 to 1.0 units per kilogram of pregnant weight, in the first, second, and third trimester, respectively. There is a transient drop in insulin required doses in the first trimester, probably because of nausea and vomiting (16).

RAPID-ACTING INSULIN ANALOGUES

Insulin lispro

In 1996, lispro became commercially available for clinical use. It is an analogue of human insulin obtained by means of recombinant DNA technology that modifies the beta-chain of human insulin by inverting the position of lysine from B29 to B28, with that of proline from B28 to B29. Insulin lispro exists naturally as a hexamer, but dissociates instantaneously into monomeric subunits when injected in the subcutaneous tissue (19).

Action begins in 15 minutes or less after the injection, and has its peak between 30-90 minutes, lasting from four to six hours. It also does not cross the placental barrier to the fetus, except with high-doses used during placental insulin studies (19). Compared with regular human insulin, its use is associated with lowering in postprandial glucose levels of 27-36 mg/dL (1.5 to 2.0 mmol/L), a 0.3% to 0.5% reduction in HbA1c, and a 20% to 30% reduction in hypoglycemic

episodes during the day, but especially during the night. Insulin lispro can be used immediately before or after a meal (19).

Insulin aspart

Insulin aspart was approved by the Food and Drug Administration for clinical use in 1999. It is also obtained by means of recombinant DNA technology, by replacing proline in the B28 position with negatively-charged aspartic acid. There is a rapid dissociation in monomers because of charge repulsion in the tertiary structure. Its action starts fifteen minutes or less after injection, and the peak is observed after 31 to 70 minutes of the injection; action lasts from 4 to 6 hours. It lowers postprandial plasma glucose by 27 mg/dL (1.5 mmol/L), HbA1c by 0.12%, and hypoglycemic episodes by 50%. Compared with regular human insulin in clinical trials performed with non-pregnant healthy volunteers, and patients with type 1 and type 2 diabetes, insulin aspart showed faster onset of action and promoted lower postprandial glucose levels (20). Insulin aspart at doses 3 to 200 times the typical human subcutaneous doses caused fetal malformations in studies of reproduction and teratology performed in animals. These adverse effects might be caused by maternal hypoglycemia occurring with these high and supraphysiological doses (21).

Insulin glulisine

Insulin glulisine is a rapid-acting analogue available for clinical use since 2004, with an action profile similar to that of insulin lispro and aspart. It is produced by replacing lysine in the B29 position by glutamic acid and asparagine in the B3 position by lysine. It has a faster onset of action and shorter duration of action than regular human insulin. It starts to act 10-15 minutes after the injection, and the peak occurs from 30-60 minutes, with its action lasting 4-5 hours. It has been shown to be as safe as insulin lispro, or to be regular in non-pregnant patients with type 1 or type 2 diabetes (21).

RAPID-ACTING INSULIN ANALOGUES IN PREGNANCY

Because of the changes in insulin needs that occur during pregnancy, short-acting insulins are generally necessary to control postprandial hyperglycemia, and to optimize the doses of intermediate-acting insulins in

order to maintain an adequate insulin basal rate. Due to their fast onset and short duration of action, rapid-acting insulin analogues are useful in pregnancy because they can reduce postprandial glucose excursions and prevent preprandial hypoglycemia. Compared with soluble human insulin outside of pregnancy, the rapid-acting analogues have been associated with better postprandial glucose control, lower HbA1c levels, and reduced risk of hypoglycemia (21).

The human placenta cannot be crossed by rapid-acting insulin analogues, as evidenced by many studies. Therefore, they can be considered as therapeutic agents in the treatment of pregnancies complicated by diabetes (18,21).

Insulin lispro

The first report on the safety and efficacy of insulin lispro in pregnancy was published in 1999; this study performed in women with gestational diabetes showed insulin lispro to be more efficacious in normalizing blood glucose levels than regular human insulin; in rapidly lowering postprandial glucose levels, and in decreasing hemoglobin A1C levels, with less hypoglycemia, and without increasing the levels of anti-insulin antibody (22). The safety and efficacy of Insulin lispro was shown in some trials, and in some case reports performed with pregnant women with gestational diabetes (22,23,25) and type 1 diabetes (24,26,27,29-32). It was also found not to cross the placenta (36). These data support that insulin lispro can be considered as a treatment option in women with gestational and type 1 diabetes that do not reach the target of glycemic control with regular human insulin (21).

In 1997, the safety of insulin lispro in pregnancy was questioned after the birth of two infants with congenital malformations whose mothers were in insulin treatment with lispro during pregnancy. This raised a question among researchers whether insulin lispro might have teratogenic effects on the fetus. Although pregnant women were excluded from the initial clinical trials testing insulin lispro, some women became unexpectedly pregnant, and 19 infants were born. Of these births, 18 children were healthy and one had congenital malformation (37). Subsequently, Wyatt and cols. performed a multicenter, multinational retrospective analysis of 500 pregnancies in which women were treated with insulin lispro before and during organogenesis; there were 27 malformed infants (5.4%); interestingly, this incidence

of malformations was not different from that found in the general population, and all children that had any kind of congenital anomaly were born to mothers who had high levels of HbA1c, at least 2 SDs above the mean of a non-diabetic population. This proved that inadequate glycemic control, instead of insulin lispro, was responsible for these malformations in this population of pregnant women with type 1 diabetes (32).

Insulin aspart

Pettitt and cols. (28) conducted the first clinical study to compare the short-term efficacy of insulin aspart, regular insulin, or no insulin in fifteen patients with gestational diabetes. Postprandial glycemic levels were significantly improved by insulin aspart compared with no exogenous and regular insulin. In a second study, the same investigators then analyzed a sample of twenty seven women randomized to receive either insulin aspart or regular insulin for prandial treatment of their hyperglycemia. Both groups maintained good glycemic control. Insulin aspart was effective in reducing postprandial glucose concentration from baseline. Insulin aspart treatment showed significantly lower C-peptide values than regular insulin, and no major hypoglycemic events were reported. Birth weight was similar in both groups with no case of macrosomia reported. This study showed that insulin aspart was comparable with regular human insulin in pregnant women with gestational diabetes regarding safety and effectiveness, and that it was more effective in providing postprandial glycemic control (38).

Recently, the largest randomized controlled clinical trial using an insulin analogue was conducted in 17 countries at 90 centers with a total of 322 type 1 diabetic women who received either regular human insulin or insulin aspart during pregnancy, with NPH (neutral protamine Hagedorn) insulin as basal-bolus insulin regimen. There have been no insulin-associated maternal or fetal complications, and no evidence that insulin aspart is teratogenic (34,35).

Insulin glulisine

There are no clinical trials using insulin glulisine in pregnancy so far, so it cannot be recommended in pregnancy (21).

Finally, it should be stated that many studies and case reports, most of them with small number of patients, have been conducted with the rapid-acting ana-

logues lispro and aspart, which have shown to be safe and effective in the treatment of pregnant women with gestational and type 1 diabetes (22-35).

Table 1 shows the results of fourteen articles reporting on 2,069 pregnant diabetic women, 1,794 with type 1 diabetes, and 275 cases of gestational diabetes. Among these patients, 831 were treated with lispro and 498 with aspart. Although not all reports were conducted comparing the outcomes found in these patients with those found in patients treated with human regular insulin, it can be concluded that both analogues, lispro and aspart, are safe and, in several aspects, more efficient than human regular insulin in the treatment of pregnant women with diabetes.

LONG-ACTING INSULIN ANALOGUES

Insulin glargine

Insulin glargine is a long-acting insulin analogue approved for use in the United States and Europe in 2000 as basal insulin. Insulin glargine has a glycine substitution in the α-chain at position 21 and two arginine molecules attached to the β-chain terminal at position 30. These changes shift the isoelectric point from pH 5.4 to 6.7, decreasing the solubility in the subcutaneous tissue and conferring greater stability and leading to longer action. It starts to act about 90 minutes after injection, action lasts 24 hours, and has no peak of ac-

tion. It lowers both fasting and postprandial glucose levels and is associated with less hypoglycemic events and lower weight gain (21).

Insulin detemir

Insulin detemir is also a long-acting insulin analogue commercially available since 2004; it is soluble and obtained by the replacement of threonine in β-chain at position 30 and the acylation of lysine at position 29 with a molecule of myristic fatty acid formed by a fourteen-carbon chain. This leads to increased hexamer stability, stronger and stable binding to albumin both at the subcutaneous injection site and in the circulation. It has a peakless action sustained for 18-20 hours, a capacity of lowering both fasting and postprandial glucose levels, and it is also associated with less hypoglycemic events and lower weight gain. The benefits of using insulin detemir, such as improved glycemic control, lower within-subject variation, reduced nocturnal hypoglycemic events and no weight gain, have been demonstrated basically in patients with type 1 diabetes (21).

LONG-ACTING INSULIN ANALOGUES IN PREGNANCY

Regarding the long-acting insulin analogues, there is a growing body of studies suggesting that they could also be helpful in the treatment of pregnant women with diabetes (21).

Table 1. Use of short-acting insulin analogues lispro and aspart in pregnancy

Studies	Number of patients	Type of DM	Lispro	Aspart	Regular	Outcomes
Jovanovic and cols. (22)	42	GDM	19	0	23	↓ PP with lispro
Bhattacharyya and cols. (23)	157	GDM	68	0	89	↓ HbA1c with lispro
Persson and cols. (24)	33	T1D	16	0	17	↓ PP and HbA1c with lispro; WR
Mecacci and cols. (25)	49	GDM	20	0	19	↓ PP with lispro
Loukovaara and cols. (26)	69	T1D	36	0	33	↓ PP and HbA1c with lispro; WR
Garg and cols. (27)	62	T1D	62	0	0	↓ HbA1c with lispro; 24% LGA; 2CM
Pettitt and cols. (28)	27	GDM	0	13	14	↓ PP with aspart
Masson and cols. (29)	76	T1D	76	0	0	6 SA; 7 LGA; 4 CM; 6 WR
Carr KJ and cols. (30)	9	T1D	9	0	0	Pre-meal = to PP insulin injection
Cypryk K and cols. (31)	71	T1D	25	46	0	No difference
Wyatt and cols. (32)	500	T1D	500	0	0	27 CM when HbA1c > 2 SD mean nl in 1st trim
Hod and cols. (33)	330	T1D	0	125	125	↓ Hypo and hyperglycemia
Mathiesen and cols. (34)	322	T1D	0	157	165	↓ PP and hypoglycemia with aspart
Hod and cols. (35)	322	T1D	0	157	165	↓ Fetal losses and preterm with aspart

T1D: type 1 *diabetes mellitus*; GDM: gestational *diabetes mellitus*; PP: postprandial glucose levels; HbA1C: glycosylated hemoglobin; LGA: large for gestational age infant; CM: congenital malformations; SA: spontaneous abortion; WR: worsening of retinopathy; SD: standard deviation.

Insulin glargine

It should be noted that insulin glargine causes a six-fold increase in IGF-I activity compared with human insulin. No large randomized clinical trials with insulin glargine used during pregnancy have been done up to now (21). It was also proven that insulin glargine does not cross the placenta (39), and many studies with small number of patients have shown the safety and efficacy of its use in pregnancy (40-54,56).

Negrato and cols. have conducted a prospective cohort study analyzing the outcomes of 56 women with pregestational and 82 with gestational diabetes treated with NPH or glargine during their pregnancies. Maternal complications were found more frequently in women with pregestational diabetes treated with NPH compared with those that were treated with glargine. In women with gestational diabetes treated with NPH, it was observed an increased incidence of new-onset pregnancy hypertension, micro- and macroalbuminuria, as well as occurrence of mild and frequent hypoglycemia, compared with those women treated with glargine. Among neonatal outcomes, significantly higher rates of NICU admission and fetal death were observed in infants born to women with pregestational diabetes treated with NPH insulin. Among infants born to women with gestational diabetes, the occurrence of jaundice and congenital malformations were significantly more frequent in the NPH-treated group *versus* the insulin glargine-treated group. These results led to the conclusion that the use of insulin glargine during pregnancy, from preconception to delivery, showed to be safe since it was associated with decreased maternal and neonatal adverse outcomes when compared with NPH insulin-treated patients (56).

Recently, Pollex and cols. have performed a meta-analysis of eight studies reporting on a total of 702 women with pregestational or gestational diabetes treated with either insulin glargine (n = 331) or NPH insulin (n = 371). There were no statistically significant differences in the occurrence of fetal outcomes with the use of insulin glargine compared with NPH insulin in these studies (58).

Insulin detemir

Animal reproduction studies have not revealed any differences between insulin detemir and human insulin regarding embryotoxicity and teratogenicity (21).

There is an ongoing randomized, controlled, open-label, multicenter, multinational trial comparing insulin detemir with NPH insulin, and both with insulin aspart, in women with type 1 diabetes planning a pregnancy (n = 306) or already pregnant (n = 164). The inclusion criteria includes diagnosis of type 1 diabetes > 12 months duration; screening HbA1c ≤ 9.0% for women recruited during prepregnancy or pregnant for 8-12 weeks, and HbA1c ≤ 8.0% at randomization. At confirmation of pregnancy, all subjects must have HbA1c ≤ 8.0%. The exclusion criteria include impaired hepatic function, cardiac problems, and uncontrolled hypertension. From the participating patients, 152 were treated with detemir, and 158 with NPH insulin. The results found so far that detemir insulin is not inferior compared with NPH insulin in pregnant women with type 1 diabetes. This study will hopefully elucidate the safety and efficacy of the basal insulin analogue detemir in diabetic pregnancy (57).

POTENTIAL RISKS ASSOCIATED WITH THE USE OF INSULIN ANALOGUES IN PREGNANCY

There are many reasons to be aware of undesirable increased IGF-1 activity during pregnancy, a period when the maternal reproductive system suffers dramatic changes to support the development of the embryo and the fetus. Important safety concerns with the use of the new insulin analogues in pregnancy have been their capacity of causing mitogenicity, immunogenicity, transplacental passage of the antibody-analogue complex and, finally, an increased risk of teratogenicity and embryotoxicity (10,21,59).

Mitogenicty was observed with the analogue Asp B10 which showed excessive development of tumors in the mammary glands in female Sprague Dawley rats. It was demonstrated that Asp B10 had increased binding affinity to IGF-I receptors (21). Insulin only crosses the placenta when linked to IGG antibodies. Therefore, insulin antibodies are a concern because they could facilitate insulin crossing of the placental barrier. However, insulin antibodies to insulin lispro and glargine have shown to be similar levels, or less frequently found when compared with regular insulins (36,39). Women with diabetes and poor glucose control present higher incidence of spontaneous miscarriage during early pregnancy probably because of malformations of the fetuses when compared with non-diabetic pregnant women. The underlying factors that contribute for the occurrence of abortions and malformations are still not clear. Possibly inherited genetic abnormalities of the fetus, lack or low levels of insulin in maternal serum

mainly in those pregnant women with type 1 diabetes, and maybe some embryotoxic effects that the diabetic serum can exert on the fetus (60).

Although not found by clinical reports thus far, there are medical reasons to be concerned about the use of insulin analogues during pregnancy because of their affinity to the IGF-I receptor: this affinity is 5.9-fold greater for insulin analogue Asp B10; 6-fold greater for insulin glargine; and 1.5-fold greater for lispro, compared with human insulin (39,58).

Alterations in IGF-I functions could cause spontaneous miscarriage, preeclampsia, and embryo defects. It is supposed that altered insulin and IGF-I serum levels could account for dysregulation of trophoblast proliferation and invasion (60). An insulin analogue that has high affinity for the IGF-I receptor, such as glargine, could exert some influence in the natural processes mediated by IGF-I. It is of note that IGF-I can bind to the insulin receptor, and insulin is capable of binding to the IGF-I receptor. However, natural insulin binds to IGF-I receptor with 1,000-fold lower affinity than insulin binding to the insulin receptor, and insulin has a 1,000-fold lower affinity for the IGF-I receptor than IGF-I (39,58).

All the new insulin analogues have modifications in their amino acid sequences. These modifications in their structure can sometimes lead to enhanced or reduced affinity for the insulin receptor and IGF-I receptor.

The long-acting insulin analogues detemir and glargine are interesting alternatives for the administration of basal insulin, but there were no clinical trials with robust results that could assess the long-term safety and efficacy of these new long-acting insulin analogues.

Table 2 shows the results of seventeen articles reporting on 1,032 pregnant diabetic women with type 1,

Table 2. Use of long-acting insulin analogues glargine and detemir in pregnancy

Studies	Number of patients	Type of DM	Glargine	Detemir	NPH	Outcomes
Devlin and cols. (40)	1	T1D	1	0		Better glycemic control *vs.* NPH
Holstein and cols. (41)	1	T1D	1	0		Better glycemic control *vs.* NPH
Woolderink and cols. (42)	7	T1D	7	0		Delivery at 37-40 weeks; no CM
Di Cianni and cols. (43)	5	T1D	5	0		No CM
Dolci and cols. (44)	1	T1D	1	0		Better glycemic control *vs.* NPH
Graves and cols. (45)	4	GDM	4	0		No nocturnal hypoglycemia
Caronna and cols. (46)	1	T1D	1	0		No adverse outcomes
Torlone and cols. (47)	6	T1D	6	0		No adverse outcomes
Pöyhönen-Alho (48)	100	T1D	42	0	49	Greater ↓ in HbA1c with glargine similar rates of glycemic control and hypoglycemia
Price and cols. (49)	32	10 T1D, 22 GDM	32	0	32	No ↑ in hypoglycemia, mean blood glucose, HbA1c, gestational age, macrosomia and neonatal morbidity
Gallen and cols. (50)	115	T1D	115	0	0	Better glycemic control with glargine < HbA1c at the end of the 1st trimester No increase in CM rates ↓ Severe hypoglycemia
Imbergamo and cols. (51)	30	T1D	15	0	15	Better glycemic control *vs.* NPH Higher frequency of femoral length < 50th percentile with glargine
Di Cianni and cols. (52)	107	T1D	107	0	0	No influence in birth weight or increase in adverse outcomes.
Fang and cols. (53)	112	T1D, T2D and 59 GDM	52	0	60	No significant differences in rates of maternal and neonatal complications ↓ macrosomia in pre-existing diabetes with glargine ↓ neonatal hypoglycemia and hyperbilirubinemia with glargine *vs.* NPH
Smith and cols. (54)	52	T1D, T2D, DMG	27	0	25	No differences in mode of delivery, average birth weight, or neonatal outcomes between glargine *vs.* NPH
Lapolla and cols. (55)	10	T1D	0	10	0	No adverse outcomes
Negrato and cols. (56)	138	T1D, T2D, 55 DMG	55	0	83	↑ rates of NICU admission and fetal death in infants born to women with pregestational diabetes NPH-treated Infants born to women with GDM, had ↑ rates of jaundice and CM in the NPH *vs.* glargine group ↓ dose of insulin and fewer maternal hypoglycemia in glargine *vs.* NPH
Mathiesen and cols. (57)	310	T1D	0	152	158	Detemir is not inferior to NPH in any of the evaluated outcomes

T1D: type 1 *diabetes mellitus*; T2D: type 2 diabetes; GDM: gestational *diabetes mellitus*; PP: postprandial glucose levels; HbA1C: glycosylated hemoglobin; CM: congenital malformations; NICU: neonatal intensive care unit; NPH: neutral protamine Hagedorn.

type 2, and gestational diabetes. Among these patients, 860 were treated with glargine, and 162 with detemir insulin. Although not all reports were conducted comparing the outcomes in these patients with those in patients treated with NPH insulin, it can be concluded that both analogues, glargine and detemir seem to be safe and in, several aspects, more efficient than NPH insulin in the treatment of diabetes in pregnancy.

Finally, it is of note that the rapid-acting analogues lispro and aspart, and the long-acting insulin detemir are assigned a use-in-pregnancy category "B" rating, meaning that clinical studies in pregnant women have not shown increased risks to the fetus. Insulin glulisine has not been evaluated in pregnancy and is assigned a category "C" rating, as well as insulin glargine, indicating that the drug should be used during pregnancy only if the potential benefits to the mother justify the potential risks to the fetus (10).

CONCLUSIONS

Pregnancies complicated by diabetes are still associated with excessive adverse fetal, neonatal, and maternal outcomes that could be avoided by optimum glycemic control. The new insulin analogues present undoubted advantages in reducing the risk of hypoglycemia, mainly during the night, and in promoting a more physiological glycemic profile in pregnant women with type 1, type 2, or gestational diabetes. The rapid-acting analogues lispro and aspart seem to be safe and efficient in reducing postprandial glucose levels even more efficiently than regular human insulin, with less hypoglycemia.

The long-acting insulin analogues do not have a pronounced peak effect as NPH insulin, and are supposed to cause less hypoglycemia, mainly during the night. However, the safety of these insulin analogues needs to be further studied and better established in pregnant women. Future studies are warranted and must also include the development of insulins that perfectly match physiological insulin profiles during pregnancy.

Disclosure: no potential conflict of interest relevant to this article was reported.

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