

## Insulin analogs and pregnancy: an update

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**Abstract** It is well known that good metabolic control maintained throughout pregnancy reduces maternal and fetal complications in diabetes. Before conception and throughout pregnancy, insulin therapy needs to be optimized and, in this context, the insulin analogs currently available in the market may help to achieve good metabolic control. We therefore review here what is known about the potential benefits and risks related to the use of these new insulins in pregnancy. Clinical and experimental data on insulin aspart and lispro strongly suggest that they have no adverse maternal or fetal effects during pregnancy in women with pregestational and gestational diabetes, and that their use results in improved glycemic control, fewer hypoglycemic episodes, and improved patient satisfaction. At present there are no published data on the use of glulisine in pregnancy. Insulin glargine during pregnancy is not recommended but, in the last years, larger surveys (retrospective and case–control studies) have been published on this field and, to date, results of about 335 pregnancies with type 1 diabetes are available showing an

incidence of congenital malformation similar to that obtained with human insulin. There are no published data concerning the use of detemir in pregnancy but the results of a prospective study are expected in 2010.

**Keywords** Diabetes · Pregnancy · Insulin analogs

### Old and new problems in the treatment of diabetic pregnancies

There is considerable evidence that glucose values play a key role in the pathogenesis of congenital malformations and perinatal complication, and that there is a positive association between poor glycemic control in the periconceptional period and the risk of the anomalies [1–4]. During the last decades thanks of a more intensive treatment of diabetes it has been observed an improvement of perinatal outcomes in the offspring of women with pre-pregnancy diabetes but epidemiological data show always an higher risk of congenital anomaly than in the general population [5–11].

In addition, in the last years other important issues are emerging, such as the long-term effects of maternal diabetes on the metabolic development of the newborn and the need of a stable “intrauterine milieu” to avoid the risk of a negative imprinting in the metabolic development of the fetus in the adult life [12, 13]. It is interesting that a normal or near-normal HbA1c is not enough to assure a “good milieu” for the development of the fetus and recent data have emphasized the role of the glucose stability not only in the pathogenesis of fetal malformations but also in perinatal complications [14, 15].

On the other hand the increase of obesity in general population and mostly in young women, and the higher

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**Table 1** Receptor binding, metabolic and mitogenic potency of currently used insulin analogs versus human insulin

Insulin type	Insulin receptor affinity	Metabolic potency	IGF-1 receptor affinity	Mytogenic potency (Saos/B10 cells)
Human insulin	100	100	100	100
Lispro	84 ± 6	82 ± 3	156 ± 16	66 ± 10
Aspart	92 ± 6	101 ± 2	81 ± 9	55 ± 22
Glargine	86	60 ± 3	641 ± 51	783 ± 13
Detemir	~18–46	~27	16 ± 1	~11

incidence of type 2 diabetes also in the adolescents, have focused the attention of diabetologists in the need of an accurate screening and a policy in the diagnosis and treatment of all pregnancies complicated by diabetes [16–18].

Recent study performed with either self-monitoring blood glucose (SMBG) or continuous glucose monitoring (CGMS) showed that in pregnancy non-complicated by diabetes, the physiological plasma glucose (PG) concentrations (fasting, overnight and premeal glucose calibrated to plasma levels) are between 50 and 99 mg% and the post-meal values (60–70 min after eating) are between 81 and 129 mg% [19, 20] (Table 1). This means that physiological PG values in pregnancy are lower than those observed out of pregnancies and that the post-prandial PG peak value is earlier (60–70 min after meal).

It is well known that a best knowledge of the pathophysiology of pregnancy, a more suitable SMBG and mostly a flexible and intensive insulin treatment with new insulin formulations (analogs) could provide better short- and long-term outcomes of all pregnancies complicated by diabetes. In this context, an optimization of insulin therapy is critical and new insulin formulation and their time action profile may be particularly useful in pregnancy. Therefore, because of their possible side-effects (potential teratogenicity, embryo toxicity, immunogenicity with transplacental passage, and mitogenicity) their use in pregnancy was limited.

In this review, we will analyze the safety and efficacy of short- and long-acting insulin analogs in pregnancy and we will try to answer to the question: are the insulin analogs a best choice for the treatment of pregnancies complicated by diabetes and, if so, are we using them in the right way?

## Insulin analogs

### Rapid-acting analogs

At present, there are three different rapid-acting insulin analogs (RAIA) on the market (lispro, aspart and glulisine).

All the three RAIA have been obtained with the technique of the recombinant DNA and by substituting or deleting one or more aminoacids in regions that does not affect the binding to the insulin receptor. As a consequence, they dissociate faster into monomers than non-modified human insulin and show an earlier and greater plasma insulin peak. Although the three RAIA are different molecules in terms of primary structure [21, 22], they exhibit similar pharmacokinetic (PK) and pharmacodynamic (PD) characteristics; the plasma insulin peak is achieved earlier and greater and post-prandial plasma glucose is better controlled than with non-modified human soluble insulin [23].

Because of their peculiar characteristics these RAIA are more able to mimic post-prandial physiological insulin secretion, and, in addition, because of the earlier waning they reduce the risk of post-prandial hypoglycemia. In clinical practice these two advantages, if associated to an adequate basal insulin can be useful in achieving a greater glucose stability and consequently a reduced glucose variability.

For these reasons, at present, the RAIA are the gold standard of mealtime insulin replacement in people with diabetes. They should substitute human soluble insulin in all diabetic subjects, provided they are combined with optimal replacement of basal insulin.

### Long-acting insulin analogs

At present two long-acting insulin analogs are available, with different structures and different PK and PD characteristics.

Glargine is a soluble long-acting insulin analog, peakless as compared to NPH, with duration of action around 24 h [24, 25]. Approved for clinical use in 2000, it is obtained by the addition of two molecules of arginine to the C-terminal of the B chain and replacing aspartic acid with glycine in position A21 to the human insulin. Glargine is present in an acidic formulation, limiting its ability to be mixed with other insulins and also possibly accounting for increased injection pain. These structural changes result in the shifting of the isoelectric point from pH 5.4 to 6.7, with a reduction in insulin solubility when injected subcutaneously, and in the capacity for dimerization: these characteristics confer a reproducible action profile, a longer action duration and reproducibility as compared with NPH [21, 26, 27]. In clinical practice this translates in a less glucose variability and in a lower risk for nocturnal hypoglycemia [21, 28, 29].

Insulin detemir is a long-acting insulin analog that is soluble at neutral pH. It is an acylated derivative of human insulin [LysB29(*N*-tetradecanoyl)des(B30) human insulin], which by a combination of increased self-association and albumin binding contributes to a protracted action,

providing a more reproducible absorption and a prolonged action profile. When compared to therapeutic doses of glargine, detemir is similarly peakless, but exhibits less longer duration of action with earlier increase in plasma glucose, free fatty acids and plasma ketones during fasting [30]. Thus, in the majority of people with T1DM, detemir should be given every 12 h. A peculiar characteristic of detemir, not shared neither by NPH nor by glargine, is that its long-term use is associated with less weight gain (0.5–1.5 kg) as compared to the other basal insulins such as NPH or glargine [31].

Similarly to glargine, the less peak-like and lower variability of detemir versus NPH results into clinical advantages, primarily lower risk for nocturnal hypoglycemia in people with T1DM [21] and T2DM [32, 33].

### The new insulins and pregnancy

The rapid-acting analog insulins, are clearly useful in pregnancy complicated by diabetes, since they are more able to reduce post-prandial hyperglycemia with respect to regular insulin. It should also be emphasized that post-prandial hyperglycemia must be reduced, as several studies have shown that this state is more predictive of adverse neonatal outcomes than fasting glycemia [34, 35].

As for long-acting insulin analogs have potential advantages in the management of pregnancy complicated by pregestational diabetes: nocturnal hypoglycemia may be an important problem in such case, due to the need to obtain and maintain the stringent glycemic target recommended in this condition [36]. Since nocturnal hypoglycemia is less common with insulin glargine, its use may be advantageous, mainly in pregnant type 1 diabetic patients.

Up to now because of the possible side-effects of the new insulins in pregnancy (their potential teratogenicity, embryo toxicity, immunogenicity with transplacental passage, and mitogenicity) their use in pregnancy was limited. The receptor binding and metabolic and mitogenic potency of insulin analogs listed in Table 1.

### Effects of the RAI in pregnancy

#### Lispro

#### Safety

Reproductive studies on animals showed no effect on fertility or teratogenic effect on the fetus after therapy with insulin lispro (LP) at a dosage four times the average dose of human insulin based on body surface area [37]. Insulin lispro has greater homology with IGF-1 than human insulin

which raised concerns of a growth-promoting effect on the fetus (Table 1). However, studies on placental transfer did not detect insulin lispro in the umbilical cords in infants after intravenous administration of insulin lispro at low dose of 0.2 units/kg per h to mothers during labor [38]. There was only a small dose-dependent transfer across human placentas delivered at term. Insulin LP was detected in the umbilicus when the mother was exposed to insulin lispro during four continuous hours of IV administration at a high concentration (=580 mU/ml) equivalent to administration of 75 units of insulin lispro [39]. In another in vitro study, a significant amount of analog accumulated in the placenta but was not detected in umbilical blood [40].

The greatest concern about the administration of insulin lispro in pregnancy resulted from a report of three cases of women who received this agent during pregnancy, and developed diabetic retinopathy by the third trimester [41]. However, two of these patients had poorly controlled diabetes at baseline with HbA1c levels that were 3.7 and 3.5% above normal and experienced a 2.2–3.6% decline in HbA1C by the third trimester. Mostly the development of retinopathy was related to the relatively rapid improvement in glucose control rather than to insulin lispro therapy. More recently a prospective, open-label study involving 69 pregnant women with type 1 diabetes revealed no differences in the frequency of diabetic retinopathy between women who received insulin lispro and those who received regular insulin during pregnancy, and glycated hemoglobin levels were significantly lower with the analog after the first trimester [42].

#### Gestational diabetes mellitus

The first randomized study which evaluated the effect of insulin lispro treatment in pregnancy was that of Jovanovic et al., in which 19 GDM patients on insulin lispro and 23 on regular insulin were studied [43]. In patients on lispro, the number (M  $\pm$  SEM) of maternal hypoglycemic episodes before breakfast (plasma glucose < 55 mg/dl) was lower than those of patients in regular insulin ( $0.65 \pm 0.1$  vs.  $0.93 \pm 1$ ,  $P < 0.02$ ). The number of episodes of post-prandial hyperglycemia (1 h plasma glucose > 120 mg/dl) were significantly lower in patients on insulin lispro than those in patients on regular insulin ( $4.0 \pm 0.4$  vs.  $5.5 \pm 0.4$ ,  $P < 0.01$ ). Moreover, treatment with lispro caused a significantly greater reduction in HbA1c levels at the third trimester:  $-5.6\%$  in treatment with lispro versus  $-2.8\%$  on regular insulin ( $P < 0.001$ ).

In subsequent papers, from Ilic et al. [44] and Bhattacharyya et al. [45] these results were confirmed and patients on insulin lispro reported greater compliance and satisfaction with this therapy, than those on regular insulin. More recently, Mecacci et al. [46] compared maternal

glucose levels and neonatal outcome in 49 GDM women randomly assigned to the treatment with regular insulin ( $n = 24$ ) or insulin lispro ( $n = 25$ ). Both types showed similar efficacy on glucose levels (2 h post-prandial, mean daily glucose values from 29 to 38 g/w =  $85.5 \pm 13$  and  $89.9 \pm$  mg/dl, respectively;  $P = ns$ ); moreover, blood glucose values (1 h post-prandial) were significantly lower in patients on insulin lispro than in those on regular insulin (mean daily glucose values from 29 to 38 g/w =  $106.9 \pm 11$  and  $123 \pm 12$  mg/dl, respectively;  $P < 0.002$ ). There were no statistically significant differences between the groups in neonatal outcome, though the number of neonates with a cranial-thoracic circumference ratio between the 10th and 25th percentiles was significantly higher in the group on regular insulin than those on insulin lispro. The last published observation from Di Cianni et al. [47] comparing LP versus aspart and human regular insulin (HI) in GDM shows better anthropometric data on infants of mothers treated with the two insulin analogs versus HI but due to the small sample size these data do not reach statistical significance. All the collected data show that, in GDM patients, insulin lispro can normalize 1 h post-prandial glucose levels better than human regular insulin and this is associated with normal anthropometric characteristics in the neonates. As regards maternal and fetal outcomes, no differences in the frequencies of cesarean sections, gestational age of delivery, preeclampsia or macrosomia were observed in GDM patients on insulin lispro compared with those on regular insulin [1, 44, 46].

### *Pregestational diabetes*

Studies regarding the effects of treatment with insulin lispro in patients with pregestational diabetes are mostly retrospective. In 31 type 1 pregnant diabetic women treated with insulin lispro, Alawi [48] reported significantly reduced levels of HbA1c, plasma glucose (1 h post-prandial) and hypoglycemic episodes, with respect to type 1 pregnant diabetic women on regular insulin ( $n = 28$ ). Garg et al. [49] in a retrospective study comprising 62 patients with type 1 diabetes on lispro found a reduction of HbA1c levels from  $7 \pm 0.2\%$  at conception to  $5.8 \pm 0.1\%$  at the time of delivery ( $P < 0.001$ ).

The studies by Bhattacharyya et al. [45], Buchbinder et al. [50] (12 patients with type 1 diabetes on lispro, 42 type 1 on regular insulin), and Persson et al. [51] (16 patients with type 1 diabetes on lispro, 17 on regular insulin) did not report significant differences in HbA1c values between treatment groups.

As regards to maternal and fetal outcomes in patients with pregestational diabetes on insulin lispro with respect to those on regular insulin, a non-significantly higher rate of cesarean sections (60 vs. 46%,  $P = ns$ ) and

hyperbilirubinemia (40 vs. 23%,  $P = ns$ ) were reported by Bhattacharyya et al. [45]. In newborns from mothers in therapy with lispro with respect to those born to mothers on regular insulin, Alawi [48] reported lower frequencies of hypoglycemic episodes at birth.

The rate of congenital anomalies in offspring of mothers treated with LP before conception and during the first trimester of pregnancies was retrospectively evaluated in the IONS Trial published on 2005 [54]. In this retrospective multinational and multicentric trial, 533 pregnancies in women treated at least 1 month before the pregnancy and for the whole first trimester were evaluated and the rate of congenital anomalies was 5.4% (currently published rates of major anomalies in infants born to mother with diabetes insulin treated are between 2.1 and 10.9%). In 2008, a sub-analysis of the IONS Italian data was published [55]. In this study, maternal and neonatal outcomes were compared with that obtained in pregnant treated with regular insulins and showed a greater improvement of first trimester HbA1c in the LP treated and a rate of congenital anomaly similar between the two groups.

Durnwald [56] recently published the first prospective observational study on LP in pregnancy (either T1 or T2), comparing 58 pregnancies treated with LP versus 49 treated with regular insulin. The LP treatment was started 3 years before the index pregnancy, baseline characteristic of the two groups were similar but the women treated with LP had a longer diabetes duration. The total insulin requirements were lower in the LP group in all the trimesters (0.58 vs. 0.67 U/kg, 0.75 vs. 1.1 U/kg, 0.98 vs. 1.25 U/kg;  $P < 0.03$ ); mean infant weight was greater in the LP group whereas the rate of large for gestational age infants and ponderal index were similar between groups. Perinatal outcomes and the malformation rates were similar in the two groups.

In conclusion, all clinical studies show that there are no differences in frequencies of preterm delivery, preeclampsia or other neonatal morbidities between pregnancies treated with LP versus human regular insulin. The results of the studies on pregestational diabetes published in the last 5 years are summarized in Table 2.

### *Aspart*

### *Safety*

Aspart has comparable receptor affinity to lispro, but in contrast, its affinity to the IGF-1 receptor is the same as human insulin (Table 1) [57]. In a 52-week study on carcinogenicity of insulin aspart there was increased incidence of mammary gland tumors, preimplantation and postimplantation fetal losses and visceral/skeletal abnormalities in female rats given insulin aspart at a dose 32 times the

**Table 2** Studies referred to use of Lispro in pregestational diabetes

Author	Pregnant women (newborns)	HbA1c at booking third trimester		Worsening of retinopathy (no. of cases)	Birth weight (g)	LGA (%)	Congenital malformations n (%)
Garg [49]	62	7.2 ± 0.2	5.8 ± 0.1	0	3,400 ± 705	24	2 (3.2)
Masson [52]	71	7.4 ± 1.7	6.17 ± 0.85	6	3,230 (1,610–4,490)	35	4 (5.6)
Cypryk [53]	25	7.8 ± 1.4	6.4 ± 0.8		3,467 ± 790		1 (4)
Wyatt [54]	496 (542)	8.9 ± 4.2	6.2 ± 2.4	Not reported	3,463 ± 765	173 (35) >4,000	27 (5.4)
Lapolla [55]	72	7.4 ± 1.7	6 ± 1.0	Not reported	3,404 ± 611	55.1	3 (4.3)
Durnwald [56]	58	7.1 ± 2.2	5.9 ± 1.0	Not reported	3,569 ± 526	32.8	4 (3.4)

average human subcutaneous dose of 1.0 U/kg per day. Human insulin had a similar effect and may have been the result of severe hypoglycemia caused by large doses of insulin. Insulin aspart was not genotoxic in a standard battery of genetic tests.

#### Gestational diabetes

Pettitt et al. [58] conducted the first clinical study to compare the short-term efficacy of insulin aspart, regular insulin, or no insulin in patients with GDM. Fifteen women with GDM and inadequate diabetes control with diet, received a standard meal test after administration of regular insulin or insulin aspart on 3 consecutive days. The postprandial glycemic control (as measured by glucose area under the curve above baseline) was significantly improved by insulin aspart compared with no exogenous insulin administered, whereas regular insulin did not show a significant difference from no exogenous insulin administered. The same investigators then observed a sample size of 27 women randomized to receive either insulin aspart or regular insulin for prandial treatment [59]. Both treatment groups maintained good overall glycemic control during the study but aspart was more effective than human insulin in reducing the post-prandial glucose concentration. Overall safety and effectiveness of aspart were comparable to human insulin in pregnant women with GDM.

#### Pregestational diabetes

The first randomized, parallel clinical multicenter trial observing the safety and efficacy of an insulin analog for the treatment of type 1 diabetes in pregnancy [60, 61] has been published recently. This trial conducted at 63 centers in 18 countries, mainly within Europe, randomized 322 type 1 diabetic women to receive either human regular insulin or insulin aspart. The main objectives were the safety, efficacy and fetal and perinatal outcomes in pregnancies treated in basal-bolus therapy with aspart and

NPH versus regular human insulin. Aspart showed a lower degree of major hypoglycemic events (1.4 vs. 2.1 episodes/year, aspart vs. HI); the risk of major/minor nocturnal hypoglycemia was 52% lower with Aspart than human regular insulin. Second and third trimester HbA1c were similar while at the end of the first and third trimester, average postprandial plasma glucose increments were significantly lower with aspart than regular insulin ( $P = 0.003$  and  $P = 0.044$ ). Maternal safety profile was similar. As regard to perinatal outcomes aspart showed lower perinatal mortality (14 vs. 22 per 1,000 births), the number of congenital malformations was 6 and 9; mean (SEM) birthweight corrected for gestational age was 3,438 and 3,555 g ( $P = 0.091$ ). Mean gestational age was 37.6 versus 37.4 weeks. Preterm delivery occurred in 20.3% (IAsp) and 30.6% (HI) of pregnancies ( $P = 0.053$ ). In conclusion, the fetal outcome using IAsp was comparable with HI with a tendency toward fewer fetal losses and preterm deliveries. The results of the studies on pregestational diabetes published in the last 5 years are summarized in Table 3.

#### Apidra

At present there are no data on safety and efficacy of apidra in pregnancies complicated by diabetes.

#### Effects of intermediate-acting insulin analogs in pregnancy

Since 3 years the intermediate-acting insulin analog neutral protamine lispro (NPL) has been commercialized. The PK characteristics of this insulin are very similar to that of NPH over a period of approximately 15 h, achieving a maximum insulin concentration approximately 6 h after dosing. There are no clinical data on its use in pregnancy but in general we could assume the same concerns regarding LP.

**Table 3** Studies referred to use of Aspart in pregestational diabetes

Author	HbA1c at booking		Total daily insulin dose (U/kg)		Hypoglycemia		Hypoglycemia	
	Aspart <i>N</i> = 157	HUM R <i>N</i> = 165	Aspart <i>N</i> = 157	HUM R <i>N</i> = 165	Major: % with episodes (rate)		Minor: % with episodes (rate)	
Mathiesen [60]	7.0 ± 0.8	6.9 ± 1.0	0.77 ± 0.27	0.78 ± 0.24	Aspart <i>N</i> = 157 24.2 (1.4)	HUM R <i>N</i> = 165 21.2 (2.1)	Aspart <i>N</i> = 157 94.3 (86.4)	HUM R <i>N</i> = 165 89.7 (94.5)
Author	Gestational age (GA) at delivery		Birth weight (g) Corrected for GA		Perinatal mortality		Preterm delivery	
	Aspart <i>N</i> = 137	HUM R <i>N</i> = 131	Aspart <i>N</i> = 137	HUM R <i>N</i> = 131	Aspart <i>N</i> = 137	HUM R <i>N</i> = 131	Aspart <i>N</i> = 137	HUM R <i>N</i> = 131
Hod [61]	37.6 ± 1.5	37.4 ± .7	3,438 ± 72	3,555 ± 73	14	22	28	41

### Effects of long-acting insulin analogs in pregnancy

#### Insulin glargine

##### Safety

The reproductive toxicity of the long-acting insulin analog glargine, evaluated in several animal studies, showed no direct effect on reproduction or embryo fetal development. However, an increased chance of abortion, intrauterine deaths and single anomalies were observed in pregnant rats and rabbits, treated with moderate to high doses of insulin glargine and insulin NPH. These effects were related to hypoglycemic episodes caused by high doses of insulin [62].

The changes in the C-terminus of the B chain insulin molecule can modify the interaction with the IGF-1 receptor, giving rise to the possibility of increased mitogenic action [63]. Receptor binding studies demonstrated that insulin glargine has a 6.5 times increased binding affinity for the IGF-1 receptor and an eightfold increased potency for stimulating DNA synthesis in human osteosarcoma cells [64]. However, the increase in mitogenic potency has not been confirmed in other studies using human diabetic muscle and *in vivo* studies performed on mice and rats, indicate that there was no increase in the incidence of mammary glands tumor using insulin glargine at high dose [65].

The higher affinity of insulin glargine for the IGF-1 receptor (Table 1) and the implication of IGF-1 as a mediator of progression of retinopathy, could suggest that the treatment with IG could be involved in the progression of diabetic retinopathy. To date, data from the literature show that rates of progression of retinopathy, proliferative retinopathy, macular edema and retinal adverse events are similar between NPH and insulin glargine [66, 67].

As a safety measure, the pharmaceutical company is performing a 5 year randomized multicenter study that compares IG and NPH insulin on the progression of

retinopathy (Clinical trials.gov identifier: NCT00174824). The study is still in progress and the data are pending.

#### Gestational diabetes

The use of insulin glargine in patients with gestational diabetes is few and, to date only two observations, including a total number of 26 patients, are available [68, 69].

The first observation [68] reports the use of insulin glargine in four women with gestational diabetes in which the decision to initiate IG was based on post-prandial self-monitored blood glucose. IG was injected in the morning, before breakfast, with an average of 29 units; the daily dose was advanced progressively by 3–5 units until 44 units at delivery (range from 10 to 50 units). The authors reported that this treatment contributed to target post-prandial and fasting glycemia without nocturnal hypoglycemia. All four women reported successful pregnancy outcome.

The second observation [69] was a case–control study. Price reported pregnancy outcomes in two groups of type 1 diabetic women, compared 22 GDM patients treated with glargine and 22 GDM control group treated with intermediate NPH insulin. In contrast, by other study on this field, the authors prescribed insulin glargine at bed time and they reported no differences in the glucose concentrations pre-lunch and pre-dinner. In the IG group, the main maternal weight gain during pregnancy was significantly lower than the corresponding control group (6.7 vs. 11.4 kg,  $P < 0.01$ ). Finally, there were no significant differences in the time and mode of delivery, birth weight and Apgar scores between two groups.

#### Pregestational diabetes

Information regarding the use of insulin glargine in pregnancy started in 2002 as case-report [70–72] and continued from 2005 to 2007 with short observational series [73–75].

**Table 4** Studies referred to use of glargine in pregestational diabetes

Author	Pregnant women (newborns)	HbA1c booking	HbA1c third trimester	Worsening of retinopathy (no. of cases)	Birth weight (g)	LGA (%)	Congenital malformations (%)
Price [69]	10	Not reported	6.9 ± 0.89	0	3,433 ± 356	40	1
Föyhönen [76]	49	7.2 ± 0.3	6.9 ± 0.2	0	3,789 ± 68	Not rep	1
Tahrani [77]	13	8.2 (6–10.9)	7.2 (5.2–10.2)	1	3,300 (1,980–4,200)	Not rep	0
Imbergamo [78]	15	7.4 ± 0.88	6.23 ± 0.86	1	3,278 ± 786	46.6	0
Gallen [79]	115	8.1 ± 0.2	6.8 ± 0.2	6	3,500 ± 600	Not rep	3
Di Cianni [80]	107	7.7 ± 1.3	6.5 ± 0.79	Not reported	3,447 ± 616	44.1	5

All these observations, involving 21 cases of type 1 pregnant women who used IG at different time of pregnancy, did not reported any adverse maternal and fetal outcomes.

More recently larger surveys (retrospective and case-control studies) have been published on this field (Table 4) and, to date, results of about 335 pregnancies with type 1 diabetes are available. Among these latter studies, the first observation is a matched case-control study by Price [69], that evaluated 20 pregnant women with type 1 diabetes, 10 treated with IG at the time of conception and during their pregnancy and 10 with an intermediate-acting human insulin. Among two groups there were no significant differences in birthweight, rates of macrosomia and neonatal morbidity. Congenital abnormalities were observed in two newborns, one in the IG and the other in the control group.

In a subsequent paper, Föyhönen-Alho [76] and colleagues reported a retrospective case-control analysis of glycemic control and pregnancy outcomes in 100 type 1 diabetic pregnancies from 3 Finnish centers, treated with IG or intermediate-acting NPH insulin prior to conception and throughout pregnancy. Although the decrease in HbA1c from the first to the third trimester of pregnancy was significantly ( $P = 0.04$ ) greater in women treated with insulin glargine, glycemic control and rate of hypoglycemia were comparable. No progression of retinopathy or nephropathy was observed in either group. In the IG group, one fetus with anencephaly was detected, leading to pregnancy termination and one fetal death occurred in each group.

An other retrospective study of all diabetic pregnancies used IG in a tertiary hospital of the UK, was performed by Tharani [77] that reported maternal and neonatal outcomes in 13 type 1 pregnant women. Of these, 11 used IG prior to conception and continued throughout pregnancy and two started IG at weeks 12 and 20 because of recurrent severe hypoglycemia. There were no malformations detected in all 13 newborns.

No differences as regard glycemic control, insulin requirement, rate of worsening of maternal diabetic complications and neonatal morbidity were observed in another retrospective study [78]. This study compared 15

type 1 diabetic pregnant women who maintained their preconception therapy with glargine and 15 with NPH insulin.

Two multicenter national surveys performed in the UK and Italy respectively, are at the moment the large studies that evaluated glycemic control and maternal-fetal outcomes in type 1 diabetic patients treated with glargine before and during pregnancy. In the British study [79], involved 115 type 1 pregnant women from 20 UK obstetric-diabetes centers, insulin glargine was used prior to pregnancy in 69% of women, started during pregnancy in 30% and stopped at booking in one patient. Mean HbA1c was 8.1% at the time of booking and progressively decreased to 6.8% at the end of pregnancy. The authors reported that retinopathy was newly diagnosed in 1% and worsened in 6%, while new-onset microalbuminuria was seen in 1% of cases. Live born babies were 109, with 6 miscarriages. Three babies had congenital malformations, corresponding to a malformation rate of 2.8% live births. If we considered that two of these occurred in women taking glargine before pregnancy, the malformation rate is 1.8% for diabetes treated with glargine during embryogenetic period. In contrast to the UK survey, in the Italian national retrospective analysis [80] regarding the use of glargine in pregnancies, all 107 type 1 diabetic women collected from 27 centers, started insulin glargine before pregnancy. In 57.4% of cases IG was stopped during the first trimester, while 42.6% of women continued using it until the end of pregnancy. In addition the authors compared the pregnancy outcome of women who were treated with IG during the entire pregnancy and women in whom IG was stopped earlier. In all the women metabolic control was improved during pregnancy. Six pregnancies were discontinued because of abortion and five newborn (4.95%) were affected by congenital abnormalities. The rates of LGA, macrosomia and ponderal index were not significantly different between women who used IG through the entire pregnancy, and those who stopped it earlier. The authors underlining this result, and suggested that the treatment with IG did not seem influence the birth weight and neonatal morbidity.

Data of reported studies, numerically not relevant and obtained by different methods, do not make a conclusion; nevertheless, the rate of congenital abnormalities in pregnant women treated with IG during embryogenetic period, is within the range (between 3.2 and 9%) for diabetic pregnancies treated with other forms of insulin, as recently reported in different European countries [5–11]. In addition studies that compared glucose control achieved with IG compared with that of NPH insulin, did not show any differences between two treatments.

Moreover, the mean birth weight in pregnancies treated with insulin glargine ranging from 3,278 to 3,789 g, with an incidence of LGA about 40%. This result is not different by others obtained in type 1 diabetic pregnant women treated with multiple daily insulin without glargine or continuous subcutaneous insulin infusion [81] and may suggest no negative effects of IG on the birth weight. Finally, although not all observations reported the status of retinopathy, the worsening of diabetic retinopathy was observed in few cases, probably more due to well-known factors that influences the course of diabetic retinopathy during pregnancy [82] (such as duration of diabetes, severity of retinopathy at conception, metabolic control, rapid improvement in glycemic control) than the use of insulin glargine. The results of the studies on pregestational diabetes published in the last 5 years are summarized in Table 4.

#### Detemir

Up to now there are no clinical studies or reports regarding the use of insulin detemir in pregnant women with diabetes. Animal reproduction studies in rabbits and rats revealed no significant differences between insulin detemir and human insulin regarding embryotoxicity and teratogenicity [83].

#### Conclusions

All the three rapid-acting insulin analogs available in the market are more effective in the early post-prandial glucose control reducing the risk of later post-prandial hypoglycemia. Therefore, studies in pregnancy are limited to lispro and aspart, both demonstrating clinical effectiveness, no evidence of teratogenesis, low antigenicity and placental transport of autoantibodies similar to human regular insulin. Lispro and aspart are assigned in the pregnancy category “B” rating, indicating that adequate clinical studies in pregnancy have not revealed increased risk to the fetus.

Data currently available on glargine in pregnancy, although not resulting from randomized controlled trials and limited to about 350 observations, show similar fetal

outcomes compared with human insulins in terms of congenital malformations. The apparent safety of glargine in pregnancy justifies the need for a large randomized controlled trial to confirm its safety and efficacy in pregnancy; up to now glargine is assigned a pregnancy category “C”.

There are no published data concerning the use of detemir in pregnancy but the results of a prospective study are expected in 2010.

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