Several clinical studies\(^1\) have shown that control of maternal glycemia before conception reduces the frequency of congenital malformations, which remain the leading cause of mortality and severe morbidity in the infants of diabetic mothers\(^2,3\). Good metabolic control throughout pregnancy can also reduce the maternal and other fetal complications typical of pregnancy complicated by diabetes\(^4\). The levels of glycemia and \(\text{HbA}_1\text{c}\) that should be achieved before conception and maintained during pregnancy, as recommended by the American Diabetes Association\(^5\), demand intensive blood glucose self-monitoring and optimized insulin therapy so that these values can be obtained with the lowest possible number of hypoglycemic episodes.

Pregnancy is characterized by changes in insulin requirements. To be more precise, the placental passage of glucose and gluconeogenic substrates causes maternal hypoglycemia in the first trimester (especially at night) and consequently the insulin dosage adopted before conception should be reduced by approximately 10%. During the second and third trimesters, the progressive increase in the production of placental contra-insulin hormones leads to a gradual increase in insulin requirements. Throughout pregnancy, moreover, blood glucose control becomes unstable, with a trend toward low fasting plasma glucose, high postprandial peaks and episodes of nocturnal hypoglycemia. Because of these changes, the dosage of short-acting insulin must be increased to cover the meal and the dosage of intermediate-acting insulin must be finely tuned to guarantee a constant basal rate without hypoglycemic episodes\(^6\).

The rapid-acting insulin analogs, i.e. lispro and aspart, may be useful because they are better able to reduce postprandial hyperglycemia than regular insulin. As for insulin glargine, its potential advantage in the management of pregnancy complicated by type 1 diabetes lies in its ability to reduce nocturnal hypoglycemia, which is particularly common in pregnant women with type 1 diabetes.

However, along with the potential benefits, the potential related risks (teratogenicity, embryo toxicity, immunogenicity with transplacental passage, mitogenicity) of using these new insulins in pregnancy must be carefully considered.

Concerning teratogenicity, studies in experimental animals have shown no embryotoxic or teratogenic effects of insulin lispro, aspart or glargine. The first report of fetal malformations in diabetic patients treated with insulin lispro involved two type 1 diabetic women\(^7\) with good metabolic control, whose therapy with insulin lispro was started before conception in one patient and in the third week of pregnancy in the other. One pregnancy was aborted at the 20th week of gestation, and the fetus had multiple cardiac malformations; the other ended in term delivery, but the infant died 3 weeks after birth from a congenital diaphragmatic hernia.

Since this first report, a series of retrospective clinical studies have been published\(^8\). As a whole, 867 pregnant diabetic women treated with insulin lispro (99% with type 1 and 1% with type 2 diabetes) and 221 pregnant diabetic women treated with regular insulin (99.5% with type 1 diabetes) can be compared. Unplanned pregnancies occurred in 41% of the diabetic pregnant women treated with insulin lispro and in 68% of those treated with regular insulin. As for the timing of the insulin therapy, 98.3% of patients were treated with lispro at the time of conception and 1.7% were transferred from regular insulin to insulin lispro between the 7th and 17th weeks of gestation due to poor metabolic control. These studies show that \(\text{HbA}_1\text{c}\) levels at conception vary considerably (from 5.2% to 13.1%). Cumulative data analysis shows that the frequency of malformations was 4.8% in patients on insulin lispro and 6.8% in those on regular insulin; this difference was non-significant (\(p = 0.3\)). More recently, a retrospective study promoted by Eli Lilly\(^9\) evaluated the outcome of pregnancy in 496 patients with pregestational diabetes from 55 centers in different parts of the world. This study examined patients...
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on insulin lispro for at least 1 month before concep-
tion and during the first trimester of pregnancy and
reported a frequency of malformations of 5.4%. Re-
Regarding insulin aspart, a randomized, controlled,
open-label trial comparing the safety and eficacy of
insulin aspart and human insulin in pregnant women
with type 1 diabetes is currently underway10. As for
insulin glargine, studies evaluating its potential terato-
genicity in humans are unfortunately very scarce: a re-
cent publication by DiCianni et al11 reported no mal-
formations or neonatal complications in five type 1
diabetic women treated with glargine during the first
weeks of pregnancy.

Studies evaluating the capacity of insulin lispro, as-
part and glargine to bind insulin-like growth factor-1
(IGF1) receptor generally report no differences with
respect to regular insulin. These results are important,
because they can be correlated with retinopathy during
pregnancy. In this context, Kitzmiller et al12 reported
the onset of proliferative retinopathy requiring laser tre-
ment in 3 diabetic women during the third trimester
of pregnancy. The authors explained this finding as
being related to the mitogenic activity of insulin lispro.
In a subsequent editorial, Jovanovic13 returned to the
cases reported by Kitzmiller et al to emphasize that the
rapid development of proliferative retinopathy in these
patients might have been due to their longstanding dia-
betes (> 6 years), to the presence of proteinuria (in one
patient), and especially to poor metabolic control, de-
monstrated by high HbA1c levels that improved rapidly
during the first few months of gestation.

Since then, a series of retrospective clinical studies
have been published on the topic, showing no progress-
ion or new onset of retinopathy in patients treated
with insulin lispro8. Importantly, pregnancy itself can
exacerbate retinopathy in cases of poor glycemic con-
trast at the beginning of the pregnancy followed by a
rapid tightening of glycemic control during the preg-
nancy. Therefore, retinopathy must be carefully moni-
tored in pregnancy.

As for immunogenicity, a relationship has been re-
ported between neonatal morbidity (and macrosomia in
particular) and placental transfer of insulin complex-
exed with antibodies8. The immunological response to
insulin lispro versus regular insulin has recently been
evaluated in women with gestational diabetes mellitus
(GDM) randomized to receive one or other type of in-
sulin during pregnancy. Anti-insulin antibody levels
were similar in the 2 groups and were within the re-
ference range except in one patient. This study showed
that insulin lispro is safe and has much the same anti-
body formation as regular human insulin8. No studies
are available in the literature on the potential immune
response to insulin aspart and glargine during preg-
nancy.

All studies assessing the possible benefits of insu-
lin lispro treatment in patients with pregestational
and gestational diabetes are retrospective8. Some
have identified significantly lower levels of HbA1c
and plasma glucose and fewer hypoglycemic episo-
des in pregnant type 1 diabetic women treated with
insulin lispro than in those on regular insulin. Con-
versely, other studies report no significant differences
in HbA1c values between treatment groups. No
studies are currently available in the literature on
maternal and fetal outcome in patients treated with
insulin aspart. For insulin glargine, the few reports
on its use in pregnancy record no maternal or neo-
atal complications8,11.

Studies assessing the effect of insulin lispro treat-
ment in women with GDM have shown a significant
reduction in hyperglycaemia before meals, postprandial
hyperglycaemia and HbA1c levels in comparison with
GDM women, treated with regular insulin8. Further-
more, Mecacci et al14 recently compared maternal glu-
cose levels and neonatal outcome in GDM women
randomly assigned to treatment with regular insulin or
insulin lispro and reported that insulin lispro was able
to normalize 1-hour postprandial glucose levels in
GDM patients, and that this reduction was associated
with normal anthropometric characteristics in the neo-
nates. The effectiveness of insulin aspart was recently
evaluated in GDM patients who were given a standard
breakfast for 3 consecutive days, with no exogenous
insulin on the first day, followed by injections of ei-
ther regular insulin or insulin aspart on the next 2 days.
The results of the study confirm the efficacy of insulin
aspart in reducing postprandial glucose concentrations
in GDM patients8.

As for maternal and fetal outcomes, no differences
in the frequency of cesarean sections, gestational age
at delivery, or frequency of preeclampsia or macrosomia
were observed in diabetic pregnant women on in-
sulin lispro versus those on regular insulin8.

In short, data in the literature analyzing the possible
adverse effects of insulin lispro suggest that this medica-
tion can be used in pregnant women with pregesta-
tional diabetes liable to postprandial hyperglycemia
and/or preprandial hypoglycemia. In our opinion, in-
formed consent should be obtained from these patients
and glucose control and retinopathy should be closely
monitored during follow-up. The efficacy of insulin
lispro in reducing postprandial glucose peaks provides
us with a new tool for treating GDM characterized by
postprandial hyperglycemia.

Insulin aspart can also be used successfully in GDM
patients with postprandial hyperglycemia. The results
of studies on insulin aspart in pregnant type 1 diabetic
women will cast further light on its use in pregnancy
in the near future.

Retrospective clinical studies on insulin glargine are
needed to establish whether it is safe to use, particu-
larly in pregnant type 1 diabetic patients, who often
have nocturnal hypoglycemia.
REFERENCES


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