PREGNANCY OUTCOMES IN WOMEN WITH TYPE 1 DIABETES TREATED WITH LONG ACTING INSULIN ANALOGS. A CASE CONTROL STUDY

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Summary. The aim was to evaluate and compare the pregnancy outcome in women with type1 diabetes (T1D) intensively treated with long acting insulin or insulin analogs. A prospective two-year case control study in ninety pregnant women with T1D was performed. The intensified treatment consisted of insulin aspart as bolus insulin and long acting insulin as basal. Women were divided into three groups according to the basal insulin: n1=30 treated with NPH insulin, n2=30 treated with insulin detemir and n3=30 treated with insulin glargine. Participants were matched for age, duration of diabetes, BMI, HbA1c before pregnancy parity, number of previous pregnancies and abortions. Metabolic control, diabetic complications, severe hypoglycemic episodes and pregnancy induced hypertension and preeclampsia were registered. Perinatal mortality, stillbirth, macrosomia, weeks and route of delivery and neonatal complications were also recorded. Statistical methods: ANOVA – with multiple comparison and chi square test have been used. No statistically significant difference in mean values for age, diabetes duration, BMI, parity, and number of previous pregnancies. No differences were observed in pre-prandial, postprandial glucose and HbA1c levels in early pregnancy (HbA1c n1 = 7.3 ± 0.8%, n2 = 6.9 ± 0.9%, n3 = 7.1 ± 0.8%, P = 0.7). No differences were observed in postprandial glucose and Hba1c in late pregnancy (HbA1c n1 = 7.8 ± 0.3%, n2 = 7.3 ± 0.6%, n3 = 7.7 ± 0.7%, P = 0.06) as well. The level of preprandial glucose in late pregnancy was lowest in first group (n1 = 4.5 ± 1.4 mmol/l, n2 = 6.6 ± 1.1 mmol/l, n3 = 6.9 ± 0.8 mmol/l, P = 0.0001). The doses of short acting insulin were significantly higher in the first group in early (n1 = 25.9 ± 34.5 U/kg, n2 = 17.0 ± 25.3 U/kg, n3 = 19.6 ± 26.7%, P = 0.004) and in late pregnancy (n1 = 41.1 ± 20.0 U/kg n2 = 26.1 ± 12.9 U/kg, n3 = 21.9 ± 10.1 U/kg, P = 0.0001). There were no differences in the dose of long acting insulin in early pregnancy between the groups, but in late pregnancy the dose in n1 group was statistically lower in comparison to the other two groups (n1 = 16.0 ± 6.8 U/kg n2 =
21.4 ± 8.2 U/kg, n3 = 29.7 ± 6.6 U/kg, P = 0.001). Severe hypoglycemic episodes in the first group were observed at rate 16% (P = 0.03). There were no differences in frequency of hypoglycemic episodes between groups n2 and n3. Caesarean section was the main choice in all groups. There was statistically significant difference in the time of delivery in the third group compared to the other groups (n1 = 36.7±1.1 week, n2 = 36.2 ± 1.2 week, n3 = 37.5 ± 0.7 week, P = 0.001). The newborn’s body weight in third group was statistically higher than in the other two groups (n3 =3623.9 ± 527.8 g, n1 = 3364.3 ± 662.4 g, n2 = 3076.7 ± 798.7 g, P = 0.02). The incidence of Respiratory Distress Syndrome was higher in the first group (P = 0.04). The frequency of spontaneous abortion and stillbirths was higher in the third group, but without statistical significance. The evaluations of risk factors could not establish relationship between the observed fetal complications and the insulin treatment. It is concluded that the treatment with long acting insulin analogs during pregnancy shows similar maternal efficacy and safety. In terms of fetal complications and safety, the conduct of longer treatment trials in larger groups is needed.

Key words: low-impact insulin analogues, diabetes mellitus type 1, pregnancy

INTRODUCTION

The pregnancy of women with T1D is a high-risk condition for both the mother and the baby. A milestone for the successful termination of pregnancy is the normoglycemic diabetes control before and during pregnancy. The Diabetes Control and Complication study (DCCT) showed that all attempts to improve diabetes control during pregnancy are limited by the high frequency of hypoglycemia [1]. In order to obtain a faster and a better glycemic control with less hypoglycemic episodes in the clinical practice, a new class insulin molecules has been introduced successfully: the insulin analogues. They have been formed via a DNA recombination technology and have a series of advantages compared to the conventional insulin. The intermediate insulin analogues Glargine (IGl) and Detemir (IDet) have no peak effect and cause less severe hypoglycemic episodes at night [2, 3].

In the IGl molecule, there are changes in both of the chains, in the α-chain the asparginate is substituted with glycine at position 21, in the β-chain, there are two additional molecules of arginine added to positions 31 and 32. The posttranslational modification in β in the chain of IGI changes the isoelectric point, slows down the absorption and increases the biological effect to more than 24 h.

In the IDet molecule, there is only a single change in the β-chain – the threonine at position 30 is removed and a 14-C myristic acid is added to the lysine, located at position 29. The acylation increases the ability for aggregation in hexamers, lowers the absorption and increases the impact up to 24 h.
The changes in the amino acid sequence of the insulin analogues influence the affinity of binding the insulin receptor to the receptor of the insulin like growth factor – 1 (IGF-1). The substitutions in the 26-30 regions of the β-chain modify the pharmacokinetic, metabolic and insulin-receptive activity [4]. The amino acid modifications in the carboxiterminal end of the β-chain at the positions 28-32 increase the stage of binding the insulin molecule to the receptor of the IGF-1. A disproportion between the metabolic and the mitogenic activity results from this binding, the time for transportation of the insulin signal in the target cells is increased and unwanted mitogenic effects arise [4].

Compared to the human insulin, IGI has similar and IDet – significantly lower affinity towards binding with the insulin receptor. The affinity to the IGF-1 receptor of IGI is 6.5 times larger than that of the human insulin and the one of IDet – significantly lower. During an in vivo survey on human muscular cells, Ciaraldi found out that IGI has the same metabolic effects as INPH and no increased mitogenic effect [5].

There is proof that the increased IGF-1 activity is unwanted during pregnancy. On one hand, IGF-1 eases implementation of the human embryo in the endometrium. On the other hand, however, disturbances in IGF-1 can cause miscarriage, preeclampsia and defects in the embryo development. It is supposed that increased insulin levels and IGF-1 may cause dysregulation in the trophoblastic invasion [6].

Intermediate acting insulin analog treatment improves the metabolic compensation before pregnancy, but can women continue their treatment with a basal insulin analog during pregnancy? There is no precise answer to this question yet. From ethic point of view, the right thing to do is to stop the analog treatment immediately and change to treatment with conventional intermediate acting insulin (INPH). The compromise related to it is the predictably high embryo-fetal risk. On the other hand, continuing the basal analog treatment is associated with unpredictably high embryo-fetal risk due to the IGF-1 related effects [6]. The wish of the pregnant women to continue their treatment with the insulin that makes them feel good helps the doctor make a decision but whether the right decision was taken can be proven only after pregnancy termination.

The aim of the present study is to compare the pregnancy outcome of pregnant women with T1D, that have been treated intensively with intermediate acting insulin analogues, considering both the mother and the child.

Design of the study A prospective, two-year long, case-control type study was performed involving 90 women with T1D. The women were selected to have good glycemic control during early pregnancy; they have been treated with intermediate acting insulin or insulin analogs in the period 2006-2008.

All pregnant women have received intensified insulin treatment with rapid acting insulin analog Aspart (IAsp) as a bolus insulin and intermediate acting insulin as a basal one. The pregnant women were divided into three groups, according to the basal insulin: n₁=30 treated with INPH insulin, n₂=30 treated with IDet and n₃=30 treated with IGI.
IAsp was applied three times within 24 hours, short before each meal [7]. The basal low-impact insulin (INPH, IDet, IGlar) was applied once before sleep at 10:00 p.m. to all women from the three groups. The insulin amounts were corrected until target normoglycemia was reached: preprandial blood glucose between 4.1-6.1 mmol/l, 2 hours postprandial blood glucose < 7.7 mmol/l and HbA1c < 7.0%. For prophylactics, folic acid was given to all women.

The efficiency of the intermediate acting insulin analog treatment was evaluated by studying the changes in the HbA1c levels in the 12 g.w. and the 36 g.w., and the safety was determined by the frequency of the severe hypoglycemic episodes occurring at night, as well as by the condition of both the mother and the newborn. The accepted criteria for severe hypoglycemia were: blood sugar ≤ 3.1 mmol/l, requiring glucose/glucagon treatment and /or help of a second/ third person.

Used statistical methods: All statistical analyses were performed using statistical package SPSS for Windows Version 11.0.1. The data were given as mean values and their standard deviations (SD), which are denoted here as „mean ± SD” or n (%). The differences among the groups are described via two tailed Student’s t test and Mann-Whitney test (for quantitative variables) and \( \chi^2 \) test (for qualitative variables). The mean values of the three groups were compared using the ANOVA procedure. For multiple comparison, the Bunferroni method was used. Differences with an empirical level of importance \( P < 0.05 \) were considered statistically true.

RESULTS

Pregnant women were selected according to the following criteria: age, diabetes duration, BMI, previous pregnancies, deliveries and abortions. After comparison of their average values, no significant differences were found among the groups considering the criteria age \( n_1 = 25.3 ± 4.4 \) r.; \( n_2 = 27.2 ± 5.2 \) r.; and \( n_3 = 25.1 ± 3.2 \) r.; \( P = 0.08 \), diabetes duration \( n_1 = 11.6 ± 6.0 \) r.; \( n_2 = 12 ± 7.0 \) r.; and \( n_3 = 9.3 ± 5.9 \) r.; \( P = 0.2 \), BMI \( n_1 = 21.3 ± 1.4 \) kg/m\(^2\); \( n_2 = 22.1 ± 1.6 \) kg/m\(^2\); and \( n_3 = 21.7 ± 0.9 \) kg/m\(^2\); \( P = 0.4 \), previous pregnancies \( n_1 = 9 (10\%); n_2 = 9 (10\%); and n_3 = 14 (15.3\%); \( P = 0.056 \) previous deliveries \( n_1 = 6 (6.6\%); n_2 = 6 (6.6\%); and n_3 = 4 (4.4\%); \( P = 0.65 \). There is tendency towards increased frequency of spontaneous abortions in previous pregnancies in the third group \( n_1 = 3/30 (10.0\%); n_2 = 3/30 (10.0\%); and n_3 = 10/30 (33.3\%); \( P = 0.049 \).

Metabolic characteristic of diabetes: All pregnancies occurred at a very good glycemic control. Levels of HbA1c < 7.0% during 12 g.w. were determined in 66/90 (73.3%) women: \( n_1 = 18/30 (60.0\%); n_2 = 25/27 (83.3\%); and n_3 = 23/30 (76.7\% \). The values of preprandial and postprandial blood glucose and HbA1c determined at the end of the first trimester in all three groups did not differ significantly [preprandial glycemia \( n_1 = 5.9±0.9 \) mmol/l, \( n_2 = 5.9 ± 1.3 \) mmol/l, \( n_3 = 5.8 ± 1.1 \) mmol/l; postprandial glycemia \( n_1 = 6.1±0.9 \) mmol/l, \( n_2 = 6.1 ± 1.3 \) mmol/l, \( n_3 = 6.0 ± 1.1 \) mmol/l].
mmol/l, P=0.6), postprandial glycemia (n₁ = 8.2 ± 1.7 mmol/l, n₂ = 7.8 ± 0.9 mmol/l, n₃ = 8.3 ± 1.4 mmol/l, P = 0.8), HbA1c (n₁ = 7.3 ± 0.8%, n₂ = 6.9 ± 0.9%, n₃ = 7.1 ± 0.8%, P = 0.7).

At the end of the third trimester, a tendency towards metabolic decompensation was observed. The postprandial glycemia and HbA1c levels increased in all women. A comparison between the mean values of postprandial glycemia and HbA1c, determined in 12 g.w. and 36 g.w. showed insignificantly positive difference [postprandial glucose (n₁ = 8.8 ± 1.2 mmol/l, n₂ = 7.9 ± 1.7 mmol/l, n₃ = 8.6 ± 0.9 mmol/l, P = 0.09); (Fig. 1); HbA1c (n₁ = 7.8 ± 0.3%, n₂ = 7.3 ± 0.6%, n₃ = 7.7 ± 0.7%, P = 0.06); (Fig. 2)]. The preprandial glucose average values in 36 g.w. for women treated with INPH were significantly lower compared to the ones determined in 12 g.w. The women treated with an insulin analogue had significantly higher preprandial glucose levels, compared to the women treated with INPH (n₁ = 4.5 ± 1.4 mmol/l, n₂ = 6.6 ± 1.1 mmol/l, n₃ = 6.9 ± 0.8 mmol/l, P = 0.0001) (Fig. 3).

**Fig. 1.** The mean HbA1 values at early and late pregnancy

**Fig. 2.** The mean values of the postprandial blood glucose at early and late pregnancy
**Insulin doses.** The average daily consumption of the IAsp increased with progressing pregnancy in all women. The IAsp doses for women from the first group were significantly higher during early and late pregnancy compared to the doses for the other two groups [12 r.c. $n_1 = 30.4 \pm 12.1$ U/24 h, $n_2 = 21.2 \pm 11.0$ U/24 h, $n_3 = 23.2 \pm 9.4$ U/24 h] ($P = 0.005$ between $n_1$ and $n_2$, $P = 0.036$ between $n_1$ and $n_3$, $P = 0$ between $n_2$ and $n_3$) and 36 g.w. ($n_1 = 41.1 \pm 20.0$ U/24 h, $n_2 = 26.1 \pm 12.9$ U/24 h, $n_3 = 21.9 \pm 10.1$ U/24 h, $P = 0.0001$) ($P = 0.01$ between $n_1$ and $n_2$, $P = 0.001$ between $n_1$ and $n_3$ and $P = 0.8$ between $n_2$ and $n_3$]). The comparison between the average doses of IAsp, determined during 12th g.w. and 36th g.w. determined a positive significant difference only in the women treated with INPH (Fig. 4).
All three groups had similar basal insulin doses during early pregnancy (n₁ = 19.9 ± 16.3 U/kg, n₂ = 21.3 ± 13.7 U/kg, n₃ = 22.2 ± 11.4 U/kg, P = 0.04). At the end of the third trimester, women treated with INPH had lower basal insulin doses, compared to the average INPH values determined during 12th and 36th g.w. which significantly differed from each other (n₁ = 16.0 ± 6.8 U/24h, n₂ = 21.4 ± 8.2 U/24h, n₃ = 29.7 ± 6.6 U/24h), (P = 0.01 between n₁ and n₂, P = 0.001 between n₁ and n₃, P = 0.057 between n₂ and n₃) (Fig. 5).

**Fig. 5.** The mean doses of the basal intermediate insulin at early and late pregnancy

**Hypoglycemic episodes.** The average frequency of hypoglycemic episodes was determined to be 5.5% (5/90). Complicated nocturnal hypoglycemia was observed only in women from the first group 5/30 (16.6%). In the other two groups, there were no severe hypoglycemias observed. In the two groups of women treated with a intermediate insulin analogue, there were only mild hypoglycemias observed, with a similar frequency of [n₂ - 6.6% (2/30) and n₃ - 10% (3/30) (P = 0.07)] (Fig. 6).

**Fig. 6.** Average body weight of the newborns
Maternal complications. There were no new complications determined in any of the 90 pregnant women observed. Preeclampsia occurred at 12/79 (15.1%) women. The severity of preeclampsia, determined according to the stage of the diurnal proteinuria was determined as mild (< 3.0 g/24 h) in 8/79 (10.1%) women and moderate (proteinuria < 5.0 g/24 h) in 4/79 (5.0%) women. There were no statistical differences in the preeclampsia frequency in women from all three groups (n₁ = 14.8% (4/27); n₂ = 11.1% (3/27) and n₃ = 12.0% (3/25); P = 0.06).

Caesarean section was the main way for birth delivery in all three groups. The average gestational age for pregnancy termination was 36.7 ± 1.2 g.w. The women of the third group were characterised by the longer duration of pregnancy (n₁ = 36.7±1.1 g.w. n₂ = 36.2 ± 1.2 g.w, n₃ = 37.5 ± 0.7 g.w., P = 0.001).

Health condition of the newborn. Out of 90 pregnancies, 79 (87.8%) were successful and were terminated with the birth of healthy children. There was no postnatal mortality of children. There are no cases registered of inborn malformations in the newborns. The average body weight of the newborns was 3 337 ± 707 g. In 9/79 (11.3%) children, the determined body weight at birth was ≥ 4000 g. The percentage of the determined macrosomia (weight ≥ 4 500 g.) was 2.5% (2/79). The children born by mothers from the third group are characterised by the highest weight (n₃ =3 623.9 ± 527.8 g, n₁ = 3 364.3 ± 662.4 g, n₂ = 3 076.7 ± 798.7 g, P = 0.02). There were four children with weight ≥ 4 500 g in this group. Risk factors analysis did not determine any significant differences between the HbA1c levels at the end of the third trimester of mothers from the third group that gave birth to children with weight ≥ 4000 g and the ones with children below ≤ 4000 g.

RDS was present in 23/79 (29.1%) newborns. The highest RDS frequency occurred in the first group, compared to the other two n₁ = 48.1% (13/27); n₂ = 18.5% (5/27) and n₃ = 20% (5/25); P = 0.04, (Fig. 7). The mothers that gave birth to children with RDS showed tendency towards increased HbA1c levels at the end of the third trimester (HbA1c .7.8 ± 0.9 compared to HbA1c 7.1 ± 0.2; P = 0.051).

![Fig. 7. Respiratory Distress Symptom frequency](image-url)
Postnatal hypoglycemia was observed at 38/79 (48.1%) newborns. Most often it occurred in mothers from the third group \( n_1 = 44.4\% \) (12/27); \( n_2 = 33.3\% \) (9/27) and \( n_3 = 68\% \) (17/25); \( P = 0.003 \) (Fig. 8).

Eleven (12.2\%) pregnancies were terminated without success. Early miscarriages were observed at 9/90 (10\%) women. Stillbirths within the time period 24-26 g.w. were observed at 2/90 (2.2\%) women. The IGI treated group is characterised by the most embryo-fetal complications (3 miscarriages and 2 stillbirths), but there was no significant difference in the determined frequencies 10.0\% (3/30); \( n_2 = 10.0\% \) (3/30) and \( n_3 = 16.6\% \) (5/30); \( P=0.08 \) (Fig.8). The risk factors analysis for the occurrence of embryo-fetal complications did not find any relationship to the HbA1c levels and the insulin treatment applied.

**Discussion** Although information on the IGI and IDet application on pregnant women can be found in the literature, to the present moment it has not been proven that their usage is harmless to the fetus and the newborn [8]. There is a comparative research on the efficiency and safety of IDet and NPH insulin for pregnant women with T1D, however it is still in the beginning [9].

The performed comparative experimental tests for embriotoxicity and teratogenicity on rodents did not find differences in the embriotoxic effect of IGI or IDet, compared to the one of INPH [10].

A few sources report on the pregnancy outcome of women treated with IG1 in the period 2002-2006 [11-16]. They all agree on the fact that IGI does not cause disturbances in the embryo-fetal development. In 2007, the results from a case study on 64 pregnant women were presented (20 women with T1D and 44 women with gestational diabetes). 32 of them were treated with IGI and 32 - with INPH. There is no significant difference in the body weight of the newborns and in the macrosomia frequency between the groups treated with IGI and INPH [17].

The results of our study presented here prove the favourable effects from intermediate acting insulin application on pregnant women with T1D. The results show that usage during pregnancy helps for a better metabolic control and a lower hypogly-
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cemic risk. Basal insulin treatment causes less uncertainty in the postprandial glycemia. IDet treatment yields the lowest degree of change in the preprandial and post-prandial blood glucose and HbA1c levels without severe nocturnal hypoglycemia.

The optimisation of the metabolic control was reached without significant uncertainties in the average daily insulin doses. At the end of the first and the third trimester, there was a similar increase in the high and intermediate insulin doses, IGI and IDet, respectively. The women treated with INPH had higher daily need of IAsp and lower need of INPH during the whole pregnancy. This was an attempt to achieve a good metabolic control with reasonably reduced risk of severe nocturnal hypoglycemia. The results obtained at the end of the third trimester for significantly lower preprandial glucose and higher hypoglycemic episode frequency do not confirm the correctness of this solution.

At the end of the third trimester, all pregnant women show tendency towards increased HbA1c levels as a result from a worsened postprandial glycemic control. This fact can be hardly explained by a wrong titration of the insulin doses. The constant increase of the bolus insulin at all women till the end of pregnancy was not a sufficient measure for achieving an optimal postprandial glycemic control. This is probably due to the increased insulin resistance, increased body weight, reduced physical activity and increased food consumption during progressing pregnancy. The pregnant women treated with IGI gave birth approximately a week later (37.5 ± 0.7 g.w.). Their newborns were characterised by significantly higher weight, where there were six children with body weight in the range between 4000 g and 4500 g. This may be a reasonable explanation for the prolonged pregnancy termination. Because of the small amount of participants, no considerable conclusions can be drawn, but it can be assumed that, even speculatively, IGI does influence the faster fetal growth, probably via secondary related IGF-1 receptor effect.

Neonatal hypoglycemia was observed at almost half of the newborns. Children from mothers treated with IGI were characterised by the highest neonatal hypoglycemia frequency compared to all other children. All newborns with weight over 4000 g had recurrent hypoglycemic episodes during the first three days after birth. It is not clear in how far the fetal hyperinsulinemia is a result from the postprandial hyperglycemia increasing at the end of the pregnancy or from a supposed treatment based IGF-1 receptor effect. Hypothetically, the effect of both factors can be considered. Eleven pregnancies all together were terminated preliminary, due to miscarriage or fetal intrauterine death. Five of the unsuccessful pregnancies were of women treated with IGI. After pregnancy termination, additional tests were performed for inherited or acquired trombophila. Inherited trombophilia was found in two of the women – one from the first group and one from the second group. Previous pregnancies of these women were also terminated with missed abortion in the 8 g.w. and the 16 g.w., respectively. Histological changes in the placental tissue of inflammation in placental blood vessels were found in the women whose pregnancy was terminated with stillbirths. Probably, the increased frequency of unfavourable embryo-fetal complications in the third group is accidental. However,
it should be mentioned that the IG1 treatment of the patients with unsuccessful pregnancies was longer than three years.

**Conclusion:** The results from the present study show that the intermediate acting insulin analogues IGI and IDet as components of the basal-bolus therapy are as efficient as the human intermediate acting insulin. As far as the safety of the fetus and the newborn is considered, further more thorough studies are necessary that should be performed on a larger number of participants.

**REFERENCES**


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