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Use of basal insulin analog detemir in pregnant women with type 1 diabetes: a case-control retrospective study

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SUMMARY: **Use of basal insulin analog detemir in pregnant women with type 1 diabetes: a case-control retrospective study.**

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Objective. *A poor glycemic control during pregnancy is associated with negative pregnancy outcomes and the frequency of pregnancy complications in women with preexisting type 1 diabetes remains high. Our aim was to evaluate retrospectively (years 2006-2011) the effectiveness and safety of insulin detemir vs NPH insulin in women with type 1 diabetes mellitus (T1DM) during pregnancy.*

Methods. *Sixteen pregnant T1DM women were included in the study. Among them, 8 maintained the previous therapy with detemir and 8 with NPH. All T1DM patients used short-acting analogs (lispro or aspart) in combination with basal insulin once daily. T1DM pregnant women were evaluated for glycemic status and presence of complications. 43 healthy pregnant women were used as control subjects for fetal and neonatal parameters.*

Results. *No statistically significant differences were detected between detemir and NPH-treated pregnant women. No fetal or neonatal parameters were statistically different in relation to the basal insulin treatment.*

Conclusions. *Insulin detemir is well tolerated as NPH with respect to both maternal parameters in pregnant women and perinatal morbidity and mortality. Although our data need to be confirmed by larger prospective studies, they suggest that insulin detemir represents a valuable option in the management of pregnant women with diabetes.*

KEY WORDS: Diabetes type 1 - Detemir - Pregnancy - Neonatal outcome - Maternal outcome.

Introduction

It is well established that poor glycemic control during pregnancy is associated with poor pregnancy outcomes (1,2) and the frequency of pregnancy complications in women with preexisting diabetes remains high (3,4). The maintenance of optimal glycemic control before conception and throughout pregnancy in women with type 1 diabetes mellitus (T1DM) is central in order both to reduce the risk of fetal malformations and to improve fetal and maternal outcomes (5). The latter goal must be balanced against the risk of maternal hypoglycemia (6), which can be a serious complication, even resulting in maternal death, and it therefore remains one of the main concerns for the treatment of pregnant women with diabetes. Other maternal complications include retinopathy, nephropathy, spontaneous abortions, pre-eclampsia, preterm delivery, and excessive weight gain. Macrosomia may complicate delivery, and the spectre of stillbirth and fetal malformations continues to generate much anxiety for the mother and her physician. Increased maternal and fetal/perinatal morbidity and mortality persist in this group, despite continuous subcutaneous insulin infusion or basal-bolus insulin regimens, the gold standard of treatment. Short-acting soluble human insulin and intermediate-acting NPH insulin have been and are being used in pregnant women with diabetes. There is unanimity for the use of rapid-acting insulin analogs in pregnant women with diabetes as potential benefits (i.e. less hypoglycemic episodes, better glycemic control and more

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flexibility in mealtime administration than human insulin) have been recognized (7-11). In regards to long-acting insulin analogs, whilst there are some evidences in the literature about glargine use in pregnant women with diabetes (12-17), very few data on insulin detemir have been reported (one case report and two case series) (18-20). In fact, both basal insulin analogs, insulin detemir and glargine, are currently category C (i.e. not recommended for use in pregnancy by the Food and Drug Administration, FDA). However, one prospective study has been conducted on insulin detemir in DMT1 pregnant women (21). Of note, previously, one large prospective randomized controlled trial has demonstrated the efficacy and safety of insulin aspart *versus* soluble human insulin, both used with NPH insulin in pregnant women with type 1 diabetes (22). Such study resulted in a change in category from C to B for the use of insulin aspart in pregnancy as recommended by the FDA.

Insulin detemir is a human insulin analog with omission of the threonine at position B30 and attachment of a 14-carbon fatty acid (myristic acid) at position B29 by acylation (23). These modifications mean that insulin detemir has a consistent pharmacokinetic/pharmacodynamic peak-less profile, with lower variability in action compared with insulin NPH and glargine in type 1 and type 2 diabetes (24-26). In numerous large-scale randomized controlled trials including patients with type 1 or type 2 diabetes, glycemic control was at least as good with insulin detemir as with NPH insulin and was associated with lower rates of hypoglycemia and less weight gain (8,10,27,28). Many women with diabetes of childbearing age who are already using insulin detemir therefore prefer to continue using it during pregnancy, with the prospect of good glycemic control and a low risk of hypoglycemia. In addition, the similarity of receptor binding properties to human insulin, as well as low mitogenic potencies of insulin detemir are of special importance to pregnant women (29,30).

Here we report a case-control study in which we retrospectively investigate neonatal outcomes and maternal metabolic parameters in pregnant women affected by T1DM treated with insulin detemir or NPH (both with mealtime short acting analogs).

Patients and methods

To evaluate retrospectively the effectiveness and safety of insulin detemir *vs* NPH we selected eight women affected by T1DM who attended consecutively our outpatients' clinic during the years 2006-2011 and had unplanned pregnancies. Forty-three healthy pregnant women (age 26.69±6.23 SD) were used as controls for fetal and neonatal outcomes. All patients with diabetes maintained insulin treatment administered before pregnancy and those using detemir gave their consent to continue the therapy. Among subjects with diabetes, eight received detemir (detemir-group, age 28.75±4.97 SD) and eight women with diabetes matched for age, weight, duration of disease and HbA1c before pregnancy received NPH (NPH-group, age 29.50±2.32 SD). Both groups were given rapid analog boluses (lispro or aspart) before meals. We excluded patients who were transferred to other hospitals during pregnancy or follow-up (no. 1), did not give their consent to continue detemir during pregnancy and therefore switched to NPH (no. 2) or had spontaneous miscarriage during the first trimester (no. 3 treated with detemir). The Institutional Review Board at the Faculty of Medicine of the University of Palermo approved the retrospective study.

In both women with diabetes and control women the following maternal parameters were assessed: age, week of delivery, weight before and at term of pregnancy, D weight, modality of delivery, presence of hypertension before pregnancy, onset of hypertension during pregnancy, gestosis in the third trimester. In the patients with diabetes we also evaluated the following: duration of diabetes; presence/absence of complications (retinopathy, nephropathy) and their progression during pregnancy; mild or severe maternal hypoglycemia; rate of recurrence of maternal ketosis; HbA1c levels at the time of conceiving and then HbA1c mean levels at each trimester (on HbA1c levels detected/evaluated every three/four weeks); fasting and post-prandial glycemic levels (2 hours after the three main meals); insulin requirement (IR) at each trimester for rapid analogs and detemir/NPH.

Concerning fetal and neonatal parameters, in both women with diabetes and control women we assessed the following: neonatal weight and length, Head Circumference (HC), Abdominal Circumference (AC) and Femoral Length (FL) at 2nd and 3rd trimester. All neonates were classified according to the Fetal Growth Curve for the Italian Population as Small for Gestational Age (SGA) when weight was below the 10th centile, Normal for Gestational Age (NGA) when weight was between the 10th and 90th centile and large for gestational age (LGA) for those above the 90th centile. Congenital abnormalities, neonatal hypoglycemia, Neonatal Respiratory Adaptation (NRA), Respiratory Distress Syndrome (RDS), neonatal hypocalcemia and neonatal jaundice were also reported. Apgar score at 1' and 5' was registered as low when ≤6 and normal when 7-10. In patients with diabetes we also performed fetal echocardiography for evaluation of the Interventricular Septal Thickness (IVS T) at the 20th and 32nd weeks of gestation.

Statistical analysis was performed using SPSS 11 software, Windows Edition (SPSS, Chicago, IL, USA). Continuous variables were analyzed as mean values±standard deviation (SD); rates and proportions were calculated for categorical data. The Kolmogorov-Smirnov test was used to verify the normality of the variables examined. As continuous variables were without normal distribution, we used non-parametric tests and the differences were analyzed using Mann-Whitney U-test. For categorical variables, the differences were analyzed using $\chi 2$-test and Fisher's exact test when appropriate. $P<0.05$ was considered statistically significant.

Results

Our study includes a total of 59 pregnant women, 16 of whom were affected by T1DM.

Among those, 8 received detemir therapy (age: 28.75±4.97 years; duration of diabetes: 12.62±6.06; pre-gravidic weight: 65.87±8.33; HbA1c at booking: 7.8±1.26) and 8 received NPH therapy (age: 29.50±2.32 years; duration of diabetes: 14.75±3.95; pre-gravidic weight: 64.5±7.09; HbA1c at booking: 8.17±1.16) (Table 1).

The remaining 43 pregnant women were healthy

TABLE 1 - MATERNAL PARAMETERS AND COMPLICATIONS IN 16 PREGNANT WOMEN WITH TYPE 1 DIABETES MELLITUS.

Maternal parameters in type 1 diabetic women					
	Detemir group No. 8		**NPH group No. 8**		
	Mean	**SD**	**Mean**	**SD**	**p**
Age (years)	28.75	4.97	29.50	2.32	0.878
Duration of diabetes (years)	12.62	6.06	14.75	3.95	0.195
Week of delivery	36.50	0.92	37.35	1.55	0.328
Pregravidic weight, Kg	65.87	8.33	64.50	7.09	0.959
After-pregnancy weight, Kg	79.87	9.38	78.96	10.75	0.798
Δ weight, Kg	14.00	3.77	14.46	4.51	0.721
	No.	**(%)**	**No.**	**(%)**	**p**
Modality of delivery					
Normal vaginal delivery	–	–	–	–	–
Elective caesarean section	8	(100)	8	(100)	
Emergency caesarean section	–	–	–	–	
Pre-gravidic hypertension	–	–	–	–	
Gravidic hypertension	–	–	3	(37.5)	0.200
Third trimester gestosis	–	–	–	–	–
Maternal complications and their progression during pregnancy					
	No.	**(%)**	**No.**	**(%)**	**p**
Diabetic retinopathy					
Non-proliferant	–	–	3	(37.5)	0.200
Proliferant	–	–	–	–	
Worsening of retinopathy	1	(12.5)	2	(25.0)	1
Microalbuminuria	–	–	–	–	–
Macroalbuminuria	–	–	–	–	
Worsening of microalbuminuria	1	(12.5)	–	–	1
Mild hypoglycaemia					
Sporadic	3	(37.5)	5	(62.5)	0.472
Frequent	3	(37.5)	1	(12.5)	
Severe hypoglycaemia	1	(12.5)	–	–	1
Frequent episodes of ketosis	1	(12.5)	2	(25.0)	1

* Significant values when $P<0.05$.

and were used as controls regarding fetal and neonatal outcomes.

No statistical difference was observed between the detemir group and the NPH group with regard to age, duration of disease, week and modality of delivery, weight before and at term of pregnancy, or complications.

The duration of pregnancy (weeks) was significantly shorter in the T1DM patients compared with the controls (detemir group 36.50±0.92, NPH group 37.35±1.55, control group 39.5±1.2 weeks, respectively; p<0.001) (Table 1).

Prevalence of elective caesarian section was significantly lower in the controls (60.4% vs. 100% of patients with diabetes, p<0.001).

Concerning the mean weight gain (Δ weight) during pregnancy, a significant statistical difference was observed between the patients with diabetes and controls (14.23±4,03 vs. 9,28±5,12 kg, p=0.002), while no difference was found between the detemir-group and the NHP-group (14±3.77 vs. 14.46±4.51 kg, p=0.721) (Table 1).

No difference was observed between the detemir and the NPH groups regarding pregravidic hypertension, third trimester gestosis, maternal complications and/or their progression during pregnancy (diabetic retinopathy, micro or macroalbuminuria), and episodes of mild hypoglycemia, severe hypoglycemia and ketosis (Table 1).

In relation to total insulin requirement (lispro/aspart and detemir or NPH) no difference was found between the detemir and NPH groups (Table 2), and no significant difference was found regarding the other metabolic parameters (HbA1c levels for each trimester, fasting and 2 hours after breakfast, lunch and dinner blood glucose) (Table 2).

In the detemir group, 1/8 neonates (14.3%) were classified as LGA, while in the NPH-group the number was 2/8 (25%) (p = NS). When compared with the control group, the prevalence of LGA was not significant considering both the detemir group (1/8 [14.3%] vs. 2/43 [4.7%]; p=0.407) and the NPH group (2/8 [25%] vs. 2/43 [4.7%], p = 0.111).

Concerning SGA, no difference was found between the detemir, NPH and control groups.

The evaluation of AC and FL during the third trimester did not suggest any statistically significant difference between the detemir, NPH and control groups (Table 3).

HC observed at the second and the third trimester showed higher frequency of cases <50th centile in the detemir group in comparison to controls (5/8 [62.5%] vs. 5/43 [11.6%], p=0.004 at the 2nd trimester; 3/8 [37.5%] vs. 3/43 [6.97%], p = 0.042). No significant difference was observed regarding HC and evaluation of Interventricular Septal Thickness (IVST) between the detemir and NPH groups (Table 3).

In both the detemir and NPH groups no difference was observed concerning neonatal outcomes (congenital malformations, neonatal hypoglycemia, neonatal respiratory adaptation, respiratory distress, neonatal jaundice, neonatal hypocalcemia and Apgar Score at 1' and 5') (Table 4).

Discussion

The majority of data published about basal insulin analogs use in pregnant women with diabetes report about insulin glargine, and among them is one previous study from our group (12-17). In general these data suggest that glargine is well tolerated and without adverse outcomes compared with NPH insulin. Only few experiences of insulin detemir use in pregnancy are found in the literature (18,19). The only published data concerning insulin detemir in pregnant women with diabetes are the case reports by Lapolla and colleagues, who sought to clarify the efficacy and safety of insulin detemir in the population of pregnant women with T1DM (18).

In our study we evaluated retrospectively the effectivenss and safety of insulin detemir vs NPH in 16 pregnant women with DMT1. Our results in this small cohort of patients (only a small number of women with diabetes carry unplanned pregnancies) showed no significant differences in regards to weight and metabolic maternal parameters during pregnancy, as well as HbA1c levels in each trimester and glycemia in different daily detections. These results confirm numerous large-scale randomized controlled trials showing that glycemic control was at least as good with insulin detemir as with NPH insulin (11).

At the same time, no difference was found concerning onset of hypoglicemia and the development of maternal complications and/or their progression. Concerning fetal parameters, a significant difference was found between the detemir and NPH groups only for fetal HC at both the second and third trimesters, while no difference was found for other biometric parameters, including IVST. No neonatal outcome malformations were observed in comparison to both the two basal insulin treated and control groups, and no difference was demonstrated for week of delivery. Also, weight at birth was similar in the detemir and the NPH group, although in the detemir group 1/8 neonates were classified as LGA versus 2/8 neonates in the NPH group. Finally, no difference was found regarding incidence of birth complications.

Animal studies in rats and rabbits have previously

TABLE 2 - INSULIN REQUIREMENT AND METABOLIC PARAMETERS IN 16 PREGNANT WOMEN WITH TYPE 1 DIABETES MELLITUS.

	Detemir group No. 8		NPH group No. 8		
	Maternal Lispro or Aspart requirement (U/Kg/die)				
	Mean	**SD**	**Mean**	**SD**	**P**
Mean of the first trimester	0.59	0.15	0.55	0.19	0.694
Mean of the second trimester	0.56	0.16	0.58	0.20	1
Mean of the third trimester	0.68	0.16	0.68	0.14	1
	Detemir or NPH requirement (U/Kg/die)				
Mean of the first trimester	0.30	0.10	0.24	0.10	0.463
Mean of the second trimester	0.29	0.13	0.27	0.12	1
Mean of the third trimester	0.32	0.11	0.31	0.12	0.959
	Total Insulin Requirement (U/Kg/die)				
Mean of the first trimester	0.91	0.11	0.79	0.27	0.694
Mean of the second trimester	0.91	0.24	0.86	0.25	0.798
Mean of the third trimester	1.02	0.22	0.96	0.21	0.721
	HbA1c (%)				
At booking	7.8	1.26	8.17	1.16	0.755
First trimester	7.38	0.99	7.60	1.33	0.779
Second trimester	6.58	0.66	6.43	0.77	0.798
Third trimester	6.77	1.24	6.32	1.15	0.798
	Fasting glucose (mmol/l)				
Mean of the first trimester	7.92	1.67	11,03	5.41	0.345
Mean of the second trimester	7.29	1.90	7.99	2.19	0.442
Mean of the third trimester	7.36	2.54	6.78	1.89	0.645
	2 hrs after breakfast glucose (mmol/l)				
Mean of the first trimester	6.59	2.28	8.30	2.2	0.228
Mean of the second trimester	6.42	2.51	6.82	1.59	0.574
Mean of the third trimester	6.84	2.14	6.17	1.88	0.328
	2 hrs after lunch glucose (mmol/l)				
Mean of the first trimester	7.92	1.99	7.35	2.33	0.573
Mean of the second trimester	5.40	1.01	6.72	1.37	0.050
Mean of the third trimester	7.08	1.24	6.61	1.48	0.442
	2 hrs after dinner glucose (mmol/l)				
Mean of the first trimester	7.24	2.81	8.79	2.84	0.491
Mean of the second trimester	6.35	0.85	6.95	1.15	0.382
Mean of the third trimester	6.90	1.03	6.46	1.98	0.195

* Significant values when P<0.05.

TABLE 3 - FETAL END NEONATAL OUTCOMES.

	Detemir group No. 8		NPH group No. 8		Control group No. 43				
	Mean	SD	Mean	SD	Mean	SD	P*	P**	P***
Neonatal weight (gr)§	3326	401	3489	572	3273	372	1	1	0.521
Neonatal Length (cm)§	50.25	4.36	48.87	1.12	49.02	1.92	0.716	0.519	1
	n°	(%)	n°	(%)	n°	(%)	P*	P**	P***
LGA	1	14.3	2	25	2	4.7	1	0.407	0.111
SGA	–	–	–	–	9	20.9	–	0.322	0.322
HC 2nd trimester									
<50th centile	5	(62.5)	3	(37.5)	5	(11.6)	0.619	0.004	0.099
>90th centile	–	–	–	–	10	(23.2)	–	0.329	0.329
HC 3nd trimester									
<50th centile	3	(37.5)	–	–	3	(6.97)	0.200	0.042	1
>90th centile	–	–	–	–	9	(20.93)	–	0.322	0.322
AC 2nd trimester									
<50th centile	6	(75)	1	(12.5)	3	(6.97)	0.040	<0.001	0.506
>90th centile	–	–	–	–	6	(13.95)	–	0.572	0.572
AC 3nd trimester									
<50th centile	2	(25)	–	–	6	(13.95)	0.466	0.595	0.572
>90th centile	1	(12.5)	2	(25)	7	(16.27)	1	1	0.627
FL 2nd trimester									
<50th centile	3	(37.5)	2	(25)	2	(4.65)	1	0.022	0.111
>90th centile	1	(12.5)	1	(12.5)	13	(30.23)	1	0.418	0.418
FL 3nd trimester									
<50th centile	1	(12.5)	–	–	1	(2.32)	1	0.291	1
>90th centile	1	(12.5)	–	–	5	(11.62)	1	1	0.579
IVST 20nd week									
<50th centile	–	–	2	(25)			0.466		
>90th centile	1	(12.5)	–	–			1		
IVST 32nd week									
<50th centile	–	–	1	(12.5)			1		
>90th centile	4	(50)	3	(37.5)			1		

p* Detemir vs. NPH; p** Detemir vs. Control; p*** NPH vs. Control
§ Bonferroni post-hoc test.
Significant values when P<0.05.

TABLE 4 - NEONATAL OUTCOMES.

	Detemir group No. 8		NPH group No. 8		
	No.	(%)	No.	(%)	p
Congenital abnormalities	–	–	–	–	–
Neonatal hypoglycaemia	–	–	–	–	–
Neonatal respiratory adaptation	–	–	–	–	–
Respiratory distress	–	–	–	–	–
Neonatal hypocalcemia	2	(25)	–	–	0.466
Neonatal jaundice	2	(25)	–	–	0.466
1-min Apgar Score					
7-10	8	(100)	8	(100)	1
≤6	–	–	–	–	
5-min Apgar Score					
7-10	8	(100)	8	(100)	1
≤6	–	–	–	–	

* Significant values when P<0.05.

shown no differences between insulin detemir and human insulin regarding embryo toxicity and teratogenicity. In addition, a low affinity of insulin detemir for the IGF-1 receptor (approximately one tenth of the human one) has been demonstrated (29).

Therefore, although data are needed regarding the affinity of insulin detemir for insulin-like growth factor-1 (IGF-1) receptor and its mitogenic stimulation as well as about progression of retinopathy, insulin detemir might be considered a suitable insulin for pregnant women also because of its potential of reducing both the adverse effects on fetal growth and the risk of rising maternal complications or their progression (above all retinopathy) (22).

In our study we have shown that insulin detemir is as well tolerated as NPH with respect to both maternal parameters in DMT1 pregnant women and perinatal morbidity and mortality.

Of course, our data need to be validated through a randomized, controlled, prospective study comparing insulin detemir with NPH insulin, both combined with insulin aspart or lispro, in pregnant women with Type 1 diabetes. However, our results indicate the insulin detemir may represent a valuable option in the management of pregnancies complicated by diabetes.

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References

1. Lepercq J, Coste J, Theau A, Dubois-Laforgue D, Timsit J. Factors associated with preterm delivery in women with type 1 diabetes: a cohort study. Diabetes Care 2004;27:2824-2828.
2. Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TR et al.; for the HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: Associations of maternal A1C and glucose with pregnancy outcomes. Diabetes Care 2012; 35:574-580.
3. Dunne FP, Avalos G, Durkan M, Mitchell Y, Gallacher T, Keenan M et al; ATLANTIC DIP collaborators. ATLANTIC DIP: pregnancy outcome for women with pregestational diabetes along the Irish Atlantic seaboard. Diabetes Care 2009; 32:1205-1206.
4. Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ 2006;333:177.
5. DCCT. Pregnancy outcomes in the Diabetes Control and Complications Trial. Am J Obstet Gynecol 1996;174:1343-1353.
6. Nielsen LR, Pedersen-Biergaard U, Thorsteinsson B, Johansen M, Damm P, Mathiesen ER. Hypoglycemia in pregnant women with type 1 diabetes: predictors and role of metabolic control. Diabetes Care 2008;31:9-14.
7. Home PD, Lindholm A, Riis A. For the European Insulin Aspart Study Group. Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial. Diabet Med 2000;17:762-770.
8. Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall MA. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia 2004;47:622-629.
9. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. Clin Ther 2004; 26:724-736.
10. Anderson JH Jr, Brunelle RL, Keohane P, Koivisto VA, Trautmann ME, Vignati L et al. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulindependent diabetes mellitus. Multicenter Insulin Lispro Study Group. Arch Intern Med 1997;157:1249-1255.
11. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med 2008;25:442-449.
12. Gallen IW, Jaap A, Roland JM, Chirayath HH. Survey of glargine use in 115 pregnant women with Type 1 diabetes. Diabet Med. 2008;25:165-169.
13. Imbergamo MP, Amato MC, Sciortino G, Gambina M, Accidenti M, Criscimanna A et al. Use of glargine in pregnant women with type 1 diabetes mellitus: a case-control study. Clin Ther 2008;30:1476-1484.
14. Fang YM, MacKeen D, Egan JF, Zelop CM. Insulin glargine compared with Neutral Protamine Hagedorn insulin in the treatment of pregnant diabetics. J Matern Fetal Neonatal Med 2009;22:249-253.
15. Di Cianni G, Torlone E, Lencioni C, Bonomo M, Di Benedetto A, Napoli A et al. For the Italian Diabetes and Pregnancy Study Group; Italian Society of Diabetology. Perinatal outcomes associated with the use of glargine during pregnancy. Diabet Med 2008;25:993-996.
16. Hofmann T, Horstmann G, Stammberger I. Evaluation of the reproductive toxicity and embryotoxicity of insulin glargine (LANTUS) in rats and rabbits. Int J Toxicol 2002;21:181-189.
17. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G. Insulin Glargine Safety in Pregnancy: a Transplacental Transfer Study. Diabetes Care 2009;33:29-33.
18. Lapolla A, Di Cianni G, Bruttomesso D, Dalfrà MG, Fresa R, Mello G et al. Use of insulin detemir in pregnancy: a report on

10 Type 1 diabetic women. Diabet Med 2009;26:1181-1182.
19. Sciacca L, Marotta V, Insalaco F, Tumminia A, Squatrito S, Vigneri R et al. Use of insulin detemir during pregnancy. Nutr Metab Cardiovasc Dis 2010;20:e15-e16.
20. Shenoy VV, Cook SJ, Parry AF, McIntyre HD. Audit of insulin detemir in pregnancy: a retrospective case series. Diabet Med 2012; doi: 10.1111/j.1464-5491.2012.03580.x.
21. Mathiesen ER, Damm P, Jovanovic L, McCance DR, Thyregod C, Jensen AB et al. Basal insulin analogues in diabetic pregnancy: a literature review and baseline results of a randomised, controlled trial in type 1 diabetes. Diabetes Metab Res Rev 2011;27:543-551.
22. Mathiesen ER, Kinsley B, Amiel SA, Heller S, McCance D, Duran S et al. For Insulin Aspart Pregnancy Study Group. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. Diabetes Care 2007;30:771-776.
23. Havelund S, Plum A, Ribel U, Jonassen I, Vølund A, Markussen J et al. The mechanism of protraction of insulin detemir, a long-acting, acylated analog of human insulin. Pharm Res 2004;21:1498-1504.
24. Heise T, Nosek L, Rønn BB, Endahl L, Heinemann L, Kapitza C et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 2004;53:1614-1620.
25. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. Diabetes Obes Metab 2007;9: 648-659.
26. Klein O, Lynge J, Endahl L, Damholt B, Nosek L, Heise T et al. Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes. Diabetes Obes Metab 2007;9:290-299.
27. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. Clin Ther 2004; 26:724-736.
28. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med 2008;25:442-449.
29. Kurtzhals P, Schäffer L, Sørensen A, Kristensen C, Jonassen I, Schmid C et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. Diabetes 2000;49:999-1005.
30. Thrailkill KM, Quattrin T, Baker L, Kuntze JE, Compton PG, Martha PM Jr. Cotherapy with recombinant human insulin-like growth factor I and insulin improves glycemic control in type 1 diabetes. RhIGF-I in IDDM Study Group. Diabetes Care 1999;22:585-592.