Insulin analogues in pregnancy and specific congenital anomalies

de Jong, Josta; Garne, Ester; Wender-Ozegowska, Ewa; Morgan, Margery; de Jong-van den Berg, Lolkje T. W.; Wang, Hao

Published in:
Diabetes-Metabolism research and reviews

DOI:
10.1002/dmrr.2730

Publication date:
2016

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2016; **32**: 366–375.
Published online 6 November 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/dmrr.2730

REVIEW ARTICLE

Insulin analogues in pregnancy and specific congenital anomalies: a literature review

Josta de Jong[1]*
Ester Garne[2]
Ewa Wender-Ozegowska[3]
Margery Morgan[4]
Lolkje T. W. de Jong-van den Berg[1]
Hao Wang[1]

[1]*Department of Pharmacoepidemiology and Pharmacoeconomics, University of Groningen, Groningen, The Netherlands*

[2]*Paediatric Department, Hospital Lillebaelt, Kolding, Denmark*

[3]*Department of Obstetrics and Women's Diseases, Poznan University of Medical Sciences, Poznań, Poland*

[4]*Congenital Anomaly Register and Information Service for Wales, Singleton Hospital, Swansea, UK*

*Correspondence to: Josta de Jong, Department of Pharmacoepidemiology and Pharmacoeconomics, University of Groningen, A. Deusinglaan 1, 9713AV Groningen, The Netherlands.
E-mail: josta.de.jong@rug.nl

The work presented in the manuscript has not been, and will not be published in whole or in part in any other journal, and is not in submission elsewhere. All authors approve of this submission of the manuscript

Received: 10 August 2015
Accepted: 11 September 2015

Summary

Insulin analogues are commonly used in pregnant women with diabetes. It is not known if the use of insulin analogues in pregnancy is associated with any higher risk of congenital anomalies in the offspring compared with use of human insulin. We performed a literature search for studies of pregnant women with pregestational diabetes using insulin analogues in the first trimester and information on congenital anomalies. The studies were analysed to compare the congenital anomaly rate among foetuses of mothers using insulin analogues with foetuses of mothers using human insulin. Of 29 studies, we included 1286 foetuses of mothers using short-acting insulin analogues with 1089 references of mothers using human insulin and 768 foetuses of mothers using long-acting insulin analogues with 685 references of mothers using long-acting human insulin (Neutral Protamine Hagedorn). The congenital anomaly rate was 4.84% and 4.29% among the foetuses of mothers using lispro and aspart. For glargine and detemir, the congenital anomaly rate was 2.86% and 3.47%, respectively. No studies on the use of insulin glulisine and degludec in pregnancy were found. There was no statistically significant difference in the congenital anomaly rate among foetuses exposed to insulin analogues (lispro, aspart, glargine or detemir) compared with those exposed to human insulin or Neutral Protamine Hagedorn insulin. The total prevalence of congenital anomalies was not increased for foetuses exposed to insulin analogues. The small samples in the included studies provided insufficient statistical power to identify a moderate increased risk of specific congenital anomalies.

Keywords insulin analogues; congenital anomalies; pregnancy; diabetes; review

Introduction

Pregnant women with pregestational type 1 or type 2 diabetes are known to have higher risks of adverse pregnancy outcomes of premature delivery, stillbirth, perinatal mortality, foetal macrosomia, respiratory distress syndrome and congenital anomalies [1,2]. Poor glycaemic control before and in the first trimester of pregnancy is associated with a higher rate of congenital anomalies [3–5]. Pregnant women with type 2 diabetes may need to switch from oral anti-diabetic medication to insulin to reach optimal glycaemic control [6,7].

Since 1996, insulin analogues that are artificial derivatives of insulin have been available. The short-acting analogues lispro, aspart and glulisine are effective within 5–20 min. The long-acting glargine, detemir and degludec are less soluble than human insulin and are slowly released from a depot in the subcutaneous tissue, resulting in stable blood levels and a longer duration of action (20–42 h) than human insulin with extended release [Neutral Protamine Hagedorn (NPH) and zinc insulin]. The combination of a short-acting analogue with a long-acting analogue has proved to cause less severe hypoglycaemia especially at night, less weight gain and better adherence and satisfaction of the patients than human insulin [8]. These advantages have resulted in the increasing use of insulin analogues in diabetic pregnant women and those planning to become pregnant.

In 1997, shortly after lispro became available on the market, two infants with multiple congenital anomalies exposed to lispro in pregnancy were reported [9]. A case report of an infant exposed to aspart in pregnancy with multiple congenital anomalies was published in 2008 [10]. These cases raised the question whether insulin analogues could have a teratogenic effect. *In vitro* studies found higher affinities of insulin analogues for the insulin growth factor 1-receptor than human insulin, which might have resulted in a higher mitogenic effect, especially for glargine. This might interfere with growth and differentiation of the foetus [11]. On the other hand, it was demonstrated that lispro and glargine were not likely to cross the placenta [12,13]. In contrast to the case reports mentioned previously, six pregnancies exposed to insulin analogues were reported that resulted in children without congenital anomalies [14–19]. No difference has been found in the congenital anomaly rate of pregnancies exposed to insulin analogues and those exposed to human insulin in several randomized controlled trials and large cohort studies [20].

Because diabetic pregnancies have higher risks of congenital anomalies compared with the general population, it is important to avoid additional risks caused by the diabetic treatment itself. The possible teratogenic effect of an anti-diabetic drug is a balance of its direct effect on the foetus and its ability to alleviate the teratogenic effect of diabetes and poor glucose control, which makes safety studies difficult. Most teratogenic exposures do not increase the prevalence of anomalies in general but have a more selective effect on specific congenital anomalies. It is not known whether there is an association between insulin analogues and specific congenital anomalies. In this literature review, we combined the results of studies on congenital anomalies among diabetic pregnancies exposed to insulin analogues in the first trimester. Our aim is to investigate if there is an increased risk of congenital anomalies among foetuses exposed to insulin analogues compared with foetuses exposed to human insulin.

Methods

Search strategy

We searched Pubmed and Embase for articles about insulin analogues, pregnancy and congenital anomalies using the following search strategy:

1. ('congenital abnormalities' [Mesh] OR 'pregnancy complications/drug therapy' OR 'pregnancy complications/drug effects' OR 'pregnancy outcome' [Mesh])
   AND
2. ('insulin/analogues and derivatives' OR 'insulin lispro' OR 'insulin aspart' OR 'insulin glargine' OR 'insulin glulisine' OR 'insulin detemir' OR 'insulin degludec').

The last searching day was 30 May 2014. From the selected studies, also, the references were searched for studies.

Selection

The inclusion criteria were as follows:

- original, non-overlapping studies including pregnancies of women with pregestational diabetes,
- exposure to insulin analogues in the first trimester ($\leq$12 weeks of gestation),
- detailed information on congenital anomalies and
- randomized controlled trials, cohort studies or observational studies with $\geq$5 exposed pregnancies.

Because teratogenic effects occur during organogenesis in the first trimester of pregnancy, studies with insulin analogue use later than the first trimester ($>$12 weeks of gestation) were excluded. In the study of Hod *et al.* [21], we only included pregnancies exposed to detemir or NPH during the whole of the first trimester. In five studies, there was no information on insulin use in the first trimester for 4–39% (in total 46) of the pregnancies, which were exposed to insulin analogues after the first trimester [22–26], and the congenital anomalies were not separately reported. We included the whole insulin analogue-exposed group, assuming that these 46 pregnancies were exposed to the same insulin analogue in the first trimester and made a corresponding remark in the footnote of the table.

DOI: 10.1002/dmrr

Data extraction

The selected studies were reclassified in five types of study designs. These could be different from the design named by the authors.

1. Randomized controlled trials.
2a. Prospective cohort studies (with reference group exposed to human insulin).
2b. Retrospective cohort studies (with reference group exposed to human insulin).
3a. Prospective exposed group (without reference group).
3b. Retrospective exposed group (without reference group).

Data analysis

The studies were analysed per individual insulin analogue. We calculated the overall rate of infants with one or more congenital anomalies (major and minor anomalies, based on the classification given in the article). We compared the rate of congenital anomalies in the insulin analogue-exposed foetuses with those exposed to human insulin (reference group). Studies including all births (live births, foetal deaths, stillbirths from 20 weeks and terminations of pregnancy) and studies including only live births were analysed separately.

The studies providing detailed information on congenital anomalies were included in the analysis of the prevalence of major anomaly subgroups. All anomalies were reclassified according to the congenital anomaly subgroups of European Surveillance of Congenital Anomalies (EUROCAT) and only included major anomalies [27]. This was checked by one of the authors (E. G.). The congenital anomalies, which were minor according to EUROCAT, were excluded. We calculated the prevalence of major congenital anomaly subgroups among foetuses exposed to insulin analogues and to human insulin. A significant higher prevalence among the foetuses exposed to insulin analogues was considered as an indication of increased risk of that specific congenital anomaly subgroup in the foetus exposed to the insulin analogue. In the congenital anomaly subgroup analysis, an infant with multiple congenital anomalies within one subgroup (e.g. combination of common arterial truncus and ventricular septal defect) was counted only once.

Statistical analysis

To compare the rate and prevalence of congenital anomalies in the foetuses exposed to insulin analogues with those exposed to human insulin, the chi-square test was used. Relative risks and 95% confidence intervals were calculated comparing the congenital anomaly rate. Microsoft® Office Excel 2010 (Microsoft® Corp., Redmond, WA, USA) and R version 3.1.0 (Free Software, Free Software Foundation, Boston, MA, USA) software were used for the data analysis. A p-value < 0.05 was considered to be statistically significant.

Results

In Pubmed and Embase, we found 342 articles of which 29 met the inclusion criteria as is shown in Figure 1. The studies were categorized per individual insulin analogue and per design as shown in Table 1.

Insulin lispro

Twelve studies with insulin lispro-exposed pregnancies were found of which nine included all births and three included only live births (Table 2). Among the 1053 foetuses exposed to insulin lispro, there were 51 who were affected by at least one congenital anomaly (4.80%). This rate was lower than the rate among the human insulin-exposed pregnancies (5.75%) but not significantly [$RR = 0.84$ (95% CI: 0.56–1.26; Table 2]. No difference was found in anomaly rates of foetuses exposed to lispro and human insulin in the separate analysis of studies including all births and studies with only live births.

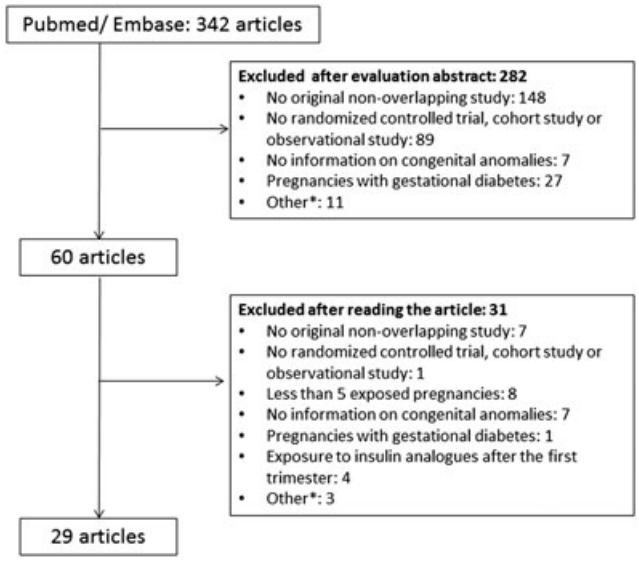

Figure 1. Selection of articles for the review. *No English language/not available/no separate information of human insulin and insulin analogue-exposed pregnancies on congenital anomalies/only human insulin use.

DOI: 10.1002/dmrr

Table 1. Numbers of selected studies categorized by insulin analogue type and design

Study design	Lispro	Aspart	Glargine	Detemir	Glulisine	Degludec	Total
1. Randomized controlled trial	0	2	0	1	0	0	3[a]
2a. Prospective cohort study	2	0	1	0	0	0	3
2b. Retrospective cohort study	7	1	7	2	0	0	17[a]
3a. Prospective-exposed group (≥5)	0	0	2	0	0	0	2
3b. Retrospective-exposed group (≥5)	3	0	5	2	0	0	10
Total	12	3	15	5	0	0	35[a]

[a]One randomized controlled trial with aspart and detemir was counted two times, one retrospective cohort study with glargine and lispro was counted two times, one retrospective cohort study with lispro, aspart, glargine and detemir was counted four times and one retrospective cohort study with glargine and detemir was counted two times.

Table 2. (a) Congenital anomalies in foetuses exposed to insulin lispro compared with human insulin

	Exposed to insulin lispro		Exposed to human insulin		p (χ^2)
	Number of foetuses	Foetuses with anomalies[a]	Number of foetuses	Foetuses with anomalies[a]	
Including all births					
García-Domínguez 2011[b] [28]	103	4	241	8	—
Chico 2010 [43]	75	3	240	16	—
Aydin 2008 [44]	10	0	23	3	—
Cypryk 2004 [45]	25	0	46	1	—
Scherbaum 2002[c] [29]	33	3	27	1	—
Bhattacharyya 2001[d] [22]	27	1	70	9	—
Negrato 2010 [46]	38	4	—	—	—
Wyatt 2004 [30]	542	29	—	—	—
Masson 2003 [31]	61	2	—	—	—
Subtotal	914	46	647	38	—
Anomaly rate %	—	5.03	—	5.87	0.54
Only live births					
Durnwald 2008 [32]	58	2	49	2	—
Garg 2003 [33]	62	2	—	—	—
Anderson 1997 [9]	19	1	—	—	—
Subtotal	139	5	49	2	—
Anomaly rate %	—	3.60	—	4.08	1
Total	1053	51	696	40	—
Anomaly rate %	—	4.84	—	5.75	0.47
				RR = 0.84 (95% CI: 0.56–1.26)	

(b) Prevalence of major congenital anomaly subgroups coded according to European Surveillance of Congenital Anomalies from foetuses exposed to insulin lispro compared with human insulin

Congenital anomaly subgroup	Lispro n = 905	Prevalence/1000	Human insulin n = 387	Prevalence/1000	p (χ^2)
Nervous system	4	4.42	1	2.58	1
Congenital heart defects	18[e]	19.89	8[f]	20.67	1
Orofacial clefts	3	3.31	0	0.00	—
Urinary	3	3.31	5	12.92	0.10
Genital	1	1.10	0	0.00	—
Limb	7	7.73	3	7.75	1
Other anomalies/syndromes	1	1.10	0	0.00	—

Mean/median HbA_{1c} values during the first trimester in separate studies could be found in supplement Table 2. Range in lispro-exposed group: 6.1–8.9% and in human insulin-exposed group: 6.0–8.3%.
References in italics: studies used for the analysis of specific congenital anomalies (Table 2).
VSD, ventricular septal defect.
[a]All malformed births as they are reported in the studies.
[b]Garcia-Dominguez: spontaneous abortions and multiple pregnancies were excluded.
[c]Scherbaum: using of lispro during pregnancy, it was not reported especially that it was used in the first trimester.
[d]Bhattacharya: one of the 27 exposed used lispro from week 14.
[e]One combination of common arterial truncus and VSD.
[f]One combination transposition of great vessels and VSD.

DOI: 10.1002/dmrr

Eight studies contained detailed information on specific congenital anomalies [9,22,28–33]. The prevalence of specific major congenital anomaly subgroups from these studies according to the EUROCAT classification is shown in Table 2. No significant difference was found between lispro and human insulin-exposed pregnancies in all subgroups of congenital anomalies. The prevalence of the subgroup relating to the nervous system was higher among the foetuses exposed to lispro compared with human insulin (4.42 vs 2.58/1000) but not significantly. The subgroup relating to congenital heart defects showed a comparable prevalence: 19.89 and 20.67 per 1000, respectively, among the lispro and human insulin-exposed foetuses. A lower prevalence of the urinary tract malformations, although not significant, was found among foetuses exposed to lispro compared with those exposed to human insulin (3.31 vs 12.92 per 1000).

Insulin aspart

We found three studies with insulin aspart exposure: two randomized controlled trials [21,34] and one retrospective cohort study [28]. Among the total of 233 foetuses exposed to insulin aspart, ten manifested a congenital anomaly, 4.29% compared with 4.33% exposed to human insulin [Table 3; *RR* = 0.99 (95% CI: 0.46–2.13)].

Among the aspart-exposed foetuses, no urinary tract anomalies were found (Table 3). The prevalence of congenital heart defects was higher in the aspart-exposed group, but not significant (34.33/1000 vs 17.81/1000; $p = 0.30$).

Insulin glargine

Fifteen studies with pregnancies exposed to insulin glargine were selected. In all studies, glargine was combined with lispro, aspart or human insulin. In the reference groups of the studies, women used NPH insulin in combination with lispro, aspart or human insulin.

Thirteen studies included all births; two included live births only. We found 595 foetuses exposed to insulin glargine, and among these were 17 with congenital anomalies (2.86%; Table 4). The anomaly rate among glargine-exposed foetuses is lower than among the foetuses exposed to NPH insulin (3.52%) but not significant [*RR* = 0.81 (95% CI: 0.40–1.65)]. Similarly, no significant difference was found in the separate analysis of studies including all births and studies with only live births.

In the analysis of specific congenital anomalies, we included 12 studies of which six found no congenital anomalies [24,35–39]. The results of the specific congenital anomalies are shown in Table 4. The prevalence of the anomaly subgroups 'nervous system' and 'congenital heart defects' among the glargine-exposed foetuses was similar to the reference group: 4.69 vs 3.02/1000; $p = 1$ and 7.04 vs 9.06/1000; $p = 1$, respectively. No

Table 3. (a) Congenital anomalies in foetuses exposed to insulin aspart compared with human insulin

	Exposed to insulin aspart		Exposed to human insulin		
	Number of foetuses	Foetuses with anomalies[a]1)	Number of foetuses	Foetuses with anomalies[a]1)	p (χ^2)
Including all births					
García-Domínguez 2011[b]2) [28]	7	0	241	8	—
Hod 2008 [34]	151	6	152	9	—
Hod 2014 [21]	75	4	—	—	—
Total	233	10	393	17	—
Anomaly rate %	—	4.29		4.33	1
				RR = 0.99 (95% CI: 0.46–2.13)	

(b) Prevalence of major congenital anomaly subgroups coded according to European Surveillance of Congenital Anomalies from pregnancies exposed to insulin aspart compared with human insulin

Congenital anomaly subgroup	Aspart $n = 233$	Prevalence/1000	Human insulin $n = 393$	Prevalence/1000	p (χ^2)
Nervous system	1	6.33	2	5.09	1
Congenital heart defects	8	34.33	7[c]	17.81	0.30
Urinary	0	0.00	4	10.18	—
Limb	0	0.00	1	2.54	—

Mean/median HbA_{1c} values during the first trimester in separate studies could be found in supplement Table 3. Range in aspart-exposed group: 6.8–6.9% and in human insulin-exposed group: 6.6–6.8%.
References in italics: studies used for the analysis of specific congenital anomalies (Table 3).
VSD, ventricular septal defect.
[a]All malformed births as they are reported in the studies.
[b]Garcia-Dominguez: spontaneous abortions and multiple pregnancies were excluded.
[c]One combination of VSD and transposition of great vessels.

DOI: 10.1002/dmrr

Table 4. (a) Congenital anomalies in foetuses exposed to insulin glargine in combination with aspart/lispro/short-acting human insulin compared with NPH insulin in combination with aspart/lispro/short-acting human insulin or CSII of aspart/lispro

	Exposed to insulin glargine		Exposed to NPH insulin		
	Number of foetuses	Foetuses with anomalies[a]	Number of foetuses	Foetuses with anomalies[a]	p (χ^2)
Including all births					
Bruttomesso 2011 [47]	44	1	—	—	—
García-Domínguez 2011[b] [28]	15	0	241	8	—
Negrato 2010 [46]	18	1	38	4	—
Fang 2009 [35]	37	0	16	0	—
Pöyhönen-Alho 2007 [48]	42	1	49	0	—
Callesen 2013[c] [49]	48	2	—	—	—
Lepercq 2010 [50]	106	2	—	—	—
Tahrani 2008[d] [23]	13	1	—	—	—
Gallen 2008[e] [25]	115	3	—	—	—
Di Cianni 2008[f] [51]	107	5	—	—	—
Cechurova 2006 [37]	7	0	—	—	—
Al-Shaikh 2006 [38]	11	0	—	—	—
Woolderink 2005[g] [24]	7	0	—	—	—
Subtotal	570	16	344	12	—
Anomaly rate %	—	2.81	—	3.49	0.70
Only live births					
Imbergano 2008 [41]	15	0	15	0	—
Price 2007 [42]	10	1	10	1	—
Subtotal	25	1	25	1	—
Anomaly rate %	—	4.00	—	4.00	1
Total	595	17	369	13	—
Anomaly rate %	—	2.86	—	3.52	0.70

(b) Prevalence of specific major congenital anomaly subgroups coded according to European Surveillance of Congenital Anomalies from foetuses exposed to insulin glargine (in combination with short-acting analogue or human insulin) compared with NPH insulin (in combination with short-acting analogue or human insulin) or CSII with short-acting analogue

Congenital anomaly subgroup	Glargine $n = 426$	Prevalence/1000	NPH $n = 331$	Prevalence/1000	p (χ^2)
Nervous system	2	4.69	1	3.02	1
Congenital heart defects	3	7.04	3[h]	9.06	1
Orofacial clefts	1	2.35	0	0.00	—
Urinary	0	0.00	4	12.08	—
Genital	1	2.35	1	3.02	1
Limb	1	2.35	0	0.00	—

Mean/median HbA_{1c} values during the first trimester in separate studies could be found in supplement Table 4. Range in glargine-exposed group: 6.7–8.1% and in human insulin-exposed group: 6.6–7.8%.
References in italics: studies used for the analysis of specific congenital anomalies (Table 4).
NPH, Neutral Protamine Hagedorn; CSII, continuous subcutaneous insulin infusion; VSD, ventricular septal defect.
[a]All malformed births as they are reported in the studies.
[b]Garcia-Dominguez: spontaneous abortions and multiple pregnancies were excluded.
[c]Callesen: reference group was group with detemir.
[d]Tharani: 11 used glargine from conception, two from second trimester.
[e]Gallen: 69% started glargine before conception, 30% later in pregnancy.
[f]Di Cianni 2008: glargine use 57.4% until 8.5 weeks.
[g]Woolderink : five glargine use from conception, one from 5 weeks, one from 27 weeks.
[h]One combination of transposition of great vessels and VSD.

urinary tract anomalies were found among the glargine-exposed foetuses.

Insulin detemir

We found five studies with insulin detemir-exposed pregnancies, of which one was a randomized controlled trial. Among the total of 173 foetuses exposed to detemir, six with congenital anomalies were found (3.47%, Table 5). No significant difference was found in anomaly rate between the foetuses exposed to detemir and those exposed to NPH insulin [3.80%; $RR = 0.91$ (95% CI: 0.35–2.39)].

In the analysis of specific anomalies, all five studies were included. The prevalence of congenital heart defects and urinary tract defects was similar between the detemir-exposed foetuses and the NPH insulin-exposed foetuses (17.34 vs 18.99/1000; $p = 1$ and 11.56 vs 12.66/1000; $p = 1$, respectively).

DOI: 10.1002/dmrr

Table 5. (a) Congenital anomalies in foetuses exposed to insulin detemir in combination with aspart/lispro/short-acting human insulin compared with NPH insulin in combination with aspart/short-acting human insulin

	Exposed to insulin detemir Number of foetuses	Exposed to insulin NPH Foetuses with anomalies[a]	Number of foetuses	Foetuses with anomalies[a]	p (χ^2)
Including all births					
Hod 2014[b] [21]	73	3	75	4	—
García-Domínguez 2011[c] [28]	1	0	241	8	—
Callesen 2013[d] [49]	71	2	—	—	—
Shenoy 2012[e] [26]	18	1	—	—	—
Lapolla 2009 [52]	10	0	—	—	—
Total	173	6	316	12	—
Anomaly rate %	—	3.47	—	3.80	1
				RR = 0.91 (95% CI: 0.35–2.39)	

(b) Prevalence of specific major congenital anomaly subgroups coded according to European Surveillance of Congenital Anomalies from foetuses exposed to insulin detemir with aspart/lispro compared with NPH/aspart or human insulin

Congenital anomaly subgroup	Detemir n = 173	Prevalence/1000	NPH n = 316	Prevalence/1000	p (χ^2)
Nervous system	0	0.00	1	3.16	—
Congenital heart defects	3	17.34	6[f]	18.99	1
Urinary	2	11.56	4	12.66	1
Genital	1	5.78	0	0.00	—

Mean/median HbA_{1c} values during the first trimester in separate studies could be found in supplement Table 2. Range in detemir-exposed group: 6.6–8.1% and in human insulin-exposed group: 6.6–7.1%.
References in italics: studies used for the analysis of specific congenital anomalies (Table 5).
NPH, Neutral Protamine Hagedorn; VSD, ventricular septal defect.
[a]All malformed births as they are reported in the studies.
[b]In the study by Hod, we used a subgroup from which it was sure that detemir had been used in the whole first trimester.
[c]Garcia-Dominguez: spontaneous abortions and multiple pregnancies were excluded.
[d]Callesen: reference group was group with glargine.
[e]Shenoy: detemir use from conception: 10, first trimester: 1, second trimester:7.
[f]One combination of transposition of great vessels and VSD.

Insulin glulisine and degludec

No studies were found involving the use of insulin glulisine and degludec in pregnancy.

Discussion

In this literature review, we found 29 studies, of which two were randomized controlled trials [21,34], describing the congenital anomalies of infants whose mothers with pregestational diabetes were exposed to insulin analogues in the first trimester of pregnancy. We found no statistically significant difference in the congenital anomaly rate among foetuses exposed to insulin analogues (lispro, aspart, glargine or detemir) compared with those exposed to human insulin or NPH insulin. The prevalence of major anomaly subgroups according to the EUROCAT classification did not differ significantly either. No studies were found on the use of the insulin glulisine and degludec during pregnancy in relation to congenital anomalies.

Our results that include the most recent studies confirm the recommendations made in the guidelines. The guideline of the National Institute for Health and Care Excellence from the UK of 2008 [7] and the 'Global Guideline Pregnancy and Diabetes' of the International Diabetes Federation of 2009 [6] considered lispro and aspart as being safe in pregnancy based on clinical studies and experience so far. Glargine and detemir were not advised to be used in pregnancy because of limited experience and lack of population-based studies. In 2012, the US Food and Drug Administration approved the use of detemir in pregnancy.

In addition, our results also indicate that there are no signals that specific congenital anomaly subgroups are related to certain insulin analogues. In most anomaly subgroups, the prevalence was comparable between a specific insulin analogue and human insulin. Less anomalies of the urinary system were found among foetuses exposed to insulin analogues than exposed to human insulin, but not to a statistically significant level. The prevalence of congenital heart defects was higher among foetuses exposed to aspart compared with human insulin, but the sample was relatively small, and the difference was not statistically significant.

The sample size of the studies, too small to detect rare congenital anomalies, was the most important limitation

DOI: 10.1002/dmrr

of this review. The relatively small samples in the included studies provide insufficient statistical power to identify a moderate risk of specific anomalies. To detect an increased risk of a specific congenital anomaly with a prevalence of 1 per 1000 or less, at least 2000 exposed and 4000 unexposed foetuses are necessary. If exposure to insulin analogues in pregnancy results in a moderate increase of rarer congenital anomalies, the sample size of each individual study included in this review, even combined, is too small to detect any teratogenic risk. In the randomized controlled trials of aspart or detemir, the total congenital anomaly rate among analogues is not higher than among foetuses exposed to human insulin, but information about specific congenital anomalies is lacking. More research with larger study populations or other study design (case–control surveillance) is needed to investigate this further.

The information summarized in this review on congenital anomalies depends particularly on the diagnosis given by the physician and the interpretation of the authors in the individual studies. In the study by Hod *et al*. [21], the diagnosis of a congenital anomaly was made by two experts who sometimes disagreed. In view of this, we reclassified the congenital anomalies according to the EUROCAT system, but the information was not always clear, and misclassifications could have been possible.

In five studies with pregnancies exposed to lispro or glargine, only live births were included [32,33,40–42]. In the analysis of lispro (Table 2), the overall congenital anomaly rate including studies with live births only was lower than that of studies including foetal deaths, stillbirths and termination of pregnancies. In the analysis of glargine (Table 4), the anomaly rates were similar. We did include studies with live births in the analysis of specific congenital anomalies, but it is possible that in these studies, some serious prenatally diagnosed congenital anomalies were missed.

An important risk factor for congenital anomalies in diabetic pregnancies is glycaemic control at conception and in the first trimester of pregnancy. This is indicated by the HbA_{1c} value [3–5]. The studies included in this review presented HbA_{1c} values in various ways: mean or median, over the entire pregnancy or for the three trimesters separately. Because of these differences in reporting HbA_{1c}s, we were not able to include them in the analysis. However, we reported the range of the HbA_{1c} values over the first trimester of pregnancy in the exposed pregnancies in a footnote of Tables 2–5 and listed them in 'supplement Tables 2, 3, 4 and 5'. The HbA_{1c} values of pregnancies exposed to insulin analogues and those exposed to human insulin were comparable. Information on possible confounders such as age, obesity and smoking was available in some studies, but, as for the HbA_{1c}, reporting in the studies was too diverse to include these parameters in the analysis.

The congenital anomaly rate and prevalence of most congenital anomaly subgroups found among foetuses exposed to insulin glargine were lower than foetuses exposed to lispro, aspart and detemir. The profile of the pregnant women in the studies of glargine might be different from those included in the studies of other insulin analogues. The studies of insulin glargine did not include randomized controlled trials and included small exposed groups without a reference group in which women were recruited from hospitals or diabetes clinics. It is possible that these diabetic mothers were better monitored than diabetic mothers from large cohorts, resulting in less congenital anomalies.

Inclusion of 46 pregnancies exposed to insulin analogues in the second or third trimester may influence our results because these pregnancies may have actually been exposed to human insulin in the first trimester as well.

In the future, larger cohort studies and randomized controlled trials are needed to confirm the safety of insulin glargine in pregnancy in relation to the risk of congenital anomalies. Studies with more exposed pregnancies with detailed information on specific congenital anomalies or case–control studies could help to gather more information on the risk of specific congenital anomalies in pregnancies exposed to aspart and detemir.

Conclusion

In this literature review, no indication of increased risk of congenital anomalies was found among the offspring of women with pregestational diabetes exposed to insulin analogues (lispro, aspart, glargine or detemir) in the first trimester of pregnancy compared with those exposed to human insulin. No studies were found assessing the risk with the insulin glulisine or degludec.

Acknowledgements

The authors wish to thank members of the EUROmediCAT Steering Group and Advisory Board for their comments on the draft manuscript.

This study was part of the EUROmediCAT research project (www.euromedicat.eu) that has been supported by the European Commission under the 7th Framework Programme Grant Agreement no. 260598.

Conflicts of interest

None declared.

Supporting information

Additional supporting information may be found in the onlinen version of this article at the publisher's web site.

References

1. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: Nationwide prospective study in the netherlands. *BMJ* 2004; **328**(7445): 915.
2. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: A large, population-based study. *Diabetes Care* 2009; **32**(11): 2005–2009.
3. Wender-Ozegowska E, Wroblewska K, Zawiejska A, Pietryga M, Szczapa J, Biczysko R. Threshold values of maternal blood glucose in early diabetic pregnancy--prediction of fetal malformations. *Acta Obstet Gynecol Scand* 2005; **84**(1): 17–25.
4. Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with type I diabetes mellitus. *Diabetologia* 2000; **43**(1): 79–82.
5. Temple R, Aldridge V, Greenwood R, Heyburn P, Sampson M, Stanley K. Association between outcome of pregnancy and glycaemic control in early pregnancy in type 1 diabetes: Population based study. *BMJ* 2002; **325**(7375): 1275–1276.
6. International Diabetes Federation. Global guideline pregnancy and diabetes. http://www.idf.org/webdata/docs/Pregnancy_EN_RTP.pdf. Updated 2009. Accessed 08/18, 2014.
7. National Institute for Health and Care Excellence (NICE). Diabetes in pregnancy: Management of diabetes and its complicationsfrom pre-conception to the postnatal period. http://www.nice.org.uk/guidance/cg63/chapter/1-Guidance?print=true. Updated 2008. Accessed 09/12, 2014.
8. Hirsch IB. Insulin analogues. *N Engl J Med* 2005; **352**(2): 174–183.
9. Diamond T, Kormas N. Possible adverse fetal effect of insulin lispro. *N Engl J Med* 1997; **337**(14): 1009; author reply 1010.
10. Kanat M, Tahtaci M. Possible fetal outcome of insulin aspart. *J Endocrinol Invest* 2008; **31**(9): 841.
11. Kurtzhals P, Schaffer L, Sorensen A, *et al*. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes* 2000; **49**(6): 999–1005.
12. Boskovic R, Feig DS, Derewlany L, Knie B, Portnoi G, Koren G. Transfer of insulin lispro across the human placenta: In vitro perfusion studies. *Diabetes Care* 2003; **26**(5): 1390–1394.
13. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G. Insulin glargine safety in pregnancy: A transplacental transfer study. *Diabetes Care* 2010; **33**(1): 29–33.
14. Stechova K, Bartaskova D, Mrstinova M, *et al*. Pregnancy in a woman suffering from type 1 diabetes associated with addison's disease and hashimoto's thyroiditis (fully developed autoimmune polyglandular syndrome type 2). *Exp Clin Endocrinol Diabetes* 2004; **112**(6): 333–337.
15. Sciacca L, Marotta V, Insalaco F, *et al*. Use of insulin detemir during pregnancy. *Nutr Metab Cardiovasc Dis* 2010; **20**(4): e15–e16.
16. Okeigwe I, Yeaton-Massey A, Kim S, Vargas JE, Murphy EJ. U-500R and aspart insulin for the treatment of severe insulin resistance in pregnancy associated with pregestational diabetes. *J Perinatol* 2013; **33**(3): 235–238.
17. Caronna S, Cioni F, Dall'Aglio E, Arsenio L. Pregnancy and the long-acting insulin analogue: A case study. *Acta Biomed* 2006; **77**(1): 24–26.
18. Dolci M, Mori M, Baccetti F. Use of glargine insulin before and during pregnancy in a woman with type 1 diabetes and addison's disease. *Diabetes Care* 2005; **28**(8): 2084–2085.
19. Holstein A, Plaschke A, Egberts EH. Use of insulin glargine during embryogenesis in a pregnant woman with type 1 diabetes. *Diabet Med* 2003; **20**(9): 779–780.
20. Lambert K, Holt RI. The use of insulin analogues in pregnancy. *Diabetes Obes Metab* 2013; **15**(10): 888–900.
21. Hod M, Mathiesen ER, Jovanovic L, *et al*. A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine hagedorn in type 1 diabetes. *J Matern Fetal Neonatal Med* 2014; **27**(1): 7–13.
22. Bhattacharyya A, Brown S, Hughes S, Vice PA. Insulin lispro and regular insulin in pregnancy. *QJM* 2001; **94**(5): 255–260.
23. Tahrani AA, Varughese GI, Wilkins JD, Taylor SE, Hanna FW. Glargine in pregnant patients with type 1 diabetes. *Diabet Med* 2008; **25**(1): 111–112.
24. Woolderink JM, van Loon AJ, Storms F, de Heide L, Hoogenberg K. Use of insulin glargine during pregnancy in seven type 1 diabetic women. *Diabetes Care* 2005; **28**(10): 2594–2595.
25. Gallen IW, Jaap A, Roland JM, Chirayath HH. Survey of glargine use in 115 pregnant women with type 1 diabetes. *Diabet Med* 2008; **25**(2): 165–169.
26. Shenoy VV, Cook SJ, Parry AF, McIntyre HD. Audit of insulin detemir in pregnancy: A retrospective case series. *Diabet Med* 2012; **29**(7): 958–959.
27. European Surveillance of Congenital Anomalies (EUROCAT). Malformation coding guides. http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/malformationcodingguides. Accessed 06/06, 2014.
28. Garcia-Dominguez M, Herranz L, Hillman N, *et al.* Use of insulin lispro during pregnancy in women with pregestational diabetes mellitus. *Med Clin (Barc)* 2011; **137**(13): 581–586.
29. Scherbaum WA, Lankisch MR, Pawlowski B, Somville T. Insulin lispro in pregnancy--retrospective analysis of 33 cases and matched controls. *Exp Clin Endocrinol Diabetes* 2002; **110**(1): 6–9.
30. Wyatt JW, Frias JL, Hoyme HE, *et al*. Congenital anomaly rate in offspring of mothers with diabetes treated with insulin lispro during pregnancy. *Diabet Med* 2005; **22**(6): 803–807.
31. Masson EA, Patmore JE, Brash PD, *et al.* Pregnancy outcome in type 1 diabetes mellitus treated with insulin lispro (humalog). *Diabet Med* 2003; **20**(1): 46–50.
32. Durnwald CP, Landon MB. A comparison of lispro and regular insulin for the management of type 1 and type 2 diabetes in pregnancy. *J Matern Fetal Neonatal Med* 2008; **21**(5): 309–313.
33. Garg SK, Frias JP, Anil S, Gottlieb PA, MacKenzie T, Jackson WE. Insulin lispro therapy in pregnancies complicated by type 1 diabetes: Glycemic control and maternal and fetal outcomes. *Endocr Pract* 2003; **9**(3): 187–193.
34. Hod M, Damm P, Kaaja R, *et al*. Fetal and perinatal outcomes in type 1 diabetes pregnancy: A randomized study comparing insulin aspart with human insulin in 322 subjects. *Am J Obstet Gynecol* 2008; **198**(2): 186.e1–186.e7.
35. 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**(3): 249–253.
36. Torlone E, Gennarini A, Ricci NB, Bolli GB. Successful use of insulin glargine during entire pregnancy until delivery in six type 1 diabetic women. *Eur J Obstet Gynecol Reprod Biol* 2007; **132**(2): 238–239.

37. Cechurova D, Lacigova S, Jankovec Z, *et al.* The insulin analog glargine during an unplanned pregnancy. *Wien Klin Wochenschr* 2006; **118**(19–20): 619–620.
38. Al-Shaikh AA. Pregnant women with type 1 diabetes mellitus treated by glargine insulin. *Saudi Med J* 2006; **27**(4): 563–565.
39. Di Cianni G, Volpe L, Lencioni C, *et al*. Use of insulin glargine during the first weeks of pregnancy in five type 1 diabetic women. *Diabetes Care* 2005; **28**(4): 982–983.
40. Devlin JT, Hothersall L, Wilkis JL. Use of insulin glargine during pregnancy in a type 1 diabetic woman. *Diabetes Care* 2002; **25**(6): 1095–1096.
41. Imbergamo MP, Amato MC, Sciortino G, *et al.* Use of glargine in pregnant women with type 1 diabetes mellitus: A case–control study. *Clin Ther* 2008; **30**(8): 1476–1484.
42. Price N, Bartlett C, Gillmer M. Use of insulin glargine during pregnancy: A case–control pilot study. *BJOG* 2007; **114**(4): 453–457.
43. Chico A, Saigi I, Garcia-Patterson A, *et al*. Glycemic control and perinatal outcomes of pregnancies complicated by type 1 diabetes: Influence of continuous subcutaneous insulin infusion and lispro insulin. *Diabetes Technol Ther* 2010; **12**(12): 937–945.
44. Aydin Y, Berker D, Direktor N, *et al*. Is insulin lispro safe in pregnant women: Does it cause any adverse outcomes on infants or mothers? *Diabetes Res Clin Pract* 2008; **80**(3): 444–448.
45. Cypryk K, Sobczak M, Pertynska-Marczewska M, *et al*. Pregnancy complications and perinatal outcome in diabetic women treated with humalog (insulin lispro) or regular human insulin during pregnancy. *Med Sci Monit* 2004; **10**(2): PI 29–32.
46. Negrato CA, Rafacho A, Negrato G, *et al.* Glargine vs. NPH insulin therapy in pregnancies complicated by diabetes: An observational cohort study. *Diabetes Res Clin Pract* 2010; **89**(1): 46–51.
47. Bruttomesso D, Bonomo M, Costa S, *et al*. Type 1 diabetes control and pregnancy outcomes in women treated with continuous subcutaneous insulin infusion (CSII) or with insulin glargine and multiple daily injections of rapid-acting insulin analogues (glargine-MDI). *Diabetes Metab* 2011; **37**(5): 426–431.
48. Poyhonen-Alho M, Ronnemaa T, Saltevo J, Ekblad U, Kaaja RJ. Use of insulin glargine during pregnancy. *Acta Obstet Gynecol Scand* 2007; **86**(10): 1171–1174.
49. Callesen NF, Damm J, Mathiesen JM, Ringholm L, Damm P, Mathiesen ER. Treatment with the long-acting insulin analogues detemir or glargine during pregnancy in women with type 1 diabetes: Comparison of glycaemic control and pregnancy outcome. *J Matern Fetal Neonatal Med* 2013; **26**(6): 588–592.
50. Lepercq J, Jacqueminet S, Hieronimus S, Timsit J, Grimaldi A. Use of insulin glargine throughout pregnancy in 102 women with type 1 diabetes. *Diabetes Metab* 2010; **36**(3): 209–212.
51. Di Cianni G, Torlone E, Lencioni C, *et al.* Perinatal outcomes associated with the use of glargine during pregnancy. *Diabet Med* 2008; **25**(8): 993–996.
52. Lapolla A, Di Cianni G, Bruttomesso D, *et al.* Use of insulin detemir in pregnancy: A report on 10 type 1 diabetic women. *Diabet Med* 2009; **26**(11): 1181–1182.