Risk of Major Congenital Malformations or Perinatal or Neonatal Death With Insulin Detemir Versus Other Basal Insulins in Pregnant Women With Preexisting Diabetes: The Real-World EVOLVE Study

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Diabetes Care 2021;44:2069–2077 | https://doi.org/10.2337/dc21-0472

OBJECTIVE

To compare the risk of severe adverse pregnancy complications in women with preexisting diabetes.

RESEARCH DESIGN AND METHODS

Multinational, prospective cohort study to assess the prevalence of newborns free from major congenital malformations or perinatal or neonatal death (primary end point) following treatment with insulin detemir (detemir) versus other basal insulins.

RESULTS

Of 1,457 women included, 727 received detemir and 730 received other basal insulins. The prevalence of newborns free from major congenital malformations or perinatal or neonatal death was similar between detemir (97.0%) and other basal insulins (95.5%) (crude risk difference 0.015 [95% CI −0.01, 0.04]; adjusted risk difference −0.003 [95% CI −0.03, 0.03]). The crude prevalence of one or more congenital malformations (major plus minor) was 9.4% vs. 12.6%, with a similar risk difference before (−0.032 [95% CI −0.064, 0.000]) and after (−0.036 [95% CI −0.081, 0.009]) adjustment for confounders. Crude data showed lower maternal HbA_{1c} during the first trimester (6.5% vs. 6.7% [48 vs. 50 mmol/mol]; estimated mean difference −0.181 [95% CI −0.300, −0.062]) and the second trimester (6.1% vs. 6.3% [43 vs. 45 mmol/mol]; −0.139 [95% CI −0.232, −0.046]) and a lower prevalence of major hypoglycemia (6.0% vs. 9.0%; risk difference −0.030 [95% CI −0.058, −0.002]), preeclampsia (6.4% vs. 10.0%; −0.036 [95% CI −0.064, −0.007]), and stillbirth (0.4% vs. 1.8%; −0.013 [95% CI −0.024, −0.002]) with detemir compared with other basal insulins. However, differences were not significant postadjustment.

CONCLUSIONS

Insulin detemir was associated with a similar risk to other basal insulins of major congenital malformations, perinatal or neonatal death, hypoglycemia, preeclampsia, and stillbirth.

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Received 26 February 2021 and accepted 24 May 2021

Clinical trial reg. no. NCT01892319, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.14769912.

Pregnant women with preexisting diabetes are at an increased risk of adverse maternal and fetal outcomes if their diabetes is not well controlled.

Long-acting insulins such as insulin detemir (detemir) and other basal insulins such as insulin glargine provide a steady background control of blood glucose levels over a long period of time, optimizing blood glucose levels with minimal risk of low blood glucose. Detemir may be better than other basal insulins at stabilizing blood glucose levels during the night. Detemir and other basal insulins are used widely to treat pregnant women with diabetes, but limited data are available on their impact on the risk of birth defects or perinatal or neonatal death in a real-world setting.

The EValuation Of LeVEmir in Pregnancy (EVOLVE) study aimed to assess the effect of detemir compared with other long-acting insulins on the risk of these severe birth outcomes in women with preexisting diabetes in a real-world setting. The study also assessed maternal HbA_{1c} levels, a measure of long-term blood-sugar control, during pregnancy and the risk of developing preeclampsia or episodes of very low blood glucose.

Pregnant women with diabetes are at an increased risk of serious complications in pregnancy, with congenital malformations or perinatal or neonatal death being the most severe (1–5). In Europe, the proportion of pregnancies, in women with diabetes, with severe congenital malformations is reported to be ~4–6% and the rate of perinatal mortality ~3% (2,3,5–9).

Optimal management of diabetes in pregnant women is required to decrease maternal hyperglycemia, while limiting hypoglycemia, in order to prevent pregnancy complications (1,5,10,11). Even small elevations in HbA_{1c} levels in early pregnancy in women with diabetes can lead to a significantly increased risk of congenital malformations (11). Insulin detemir (detemir) is a long-acting basal insulin analog with slow absorption rates and a prolonged metabolic effect (12,13). It has a more consistent effect on fasting plasma glucose levels (less day-to-day variability in the glucose-lowering profile) than NPH insulin (12) or insulin glargine (14,15), which may improve the probability of reaching target HbA_{1c} levels, lowering the risk of severe hypoglycemia and congenital malformations. Outside of pregnancy, long-acting insulin analogs improve glycemic control, with lower associated rates of hypoglycemia than NPH insulin (16,17). Among the basal insulin analogs, the European Union prescribing labels for both detemir and insulin glargine allow for consideration of use in pregnancy (18,19), and insulin analogs are now widely used in pregnant women (20,21).

There are limited prospective data available on the use of detemir and other basal insulins in pregnancy. A single randomized controlled trial (RCT) investigated the use of detemir versus NPH insulin, both in combination with insulin aspart, in pregnant women with type 1 diabetes (22). The data showed significant improvements in fasting plasma glucose with detemir compared with NPH insulin, with similar HbA_{1c} levels and rates of hypoglycemia (22), and suggested that both insulins had a good safety profile with regard to perinatal outcomes (23). While RCTs give the best scientific evidence for more common outcomes, prospective cohort studies provide important real-world data for rare events such as congenital malformations and perinatal or neonatal mortality. Different insulin analogs have been shown to vary in their affinities to growth factor receptors, and the safety implications of this are unclear (24); whether this may relate to prevalence of congenital malformations has not previously been investigated in prospective studies. Stillbirths, which are the main component of perinatal mortality, are known to be related to poor glycemic control (7).

Against this background, the European Medicines Agency (EMA) therefore finds a need for large observational studies using real-world data to assess the effect of long-acting basal insulin analogs on the risk of these severe complications in pregnant women with diabetes. Data on maternal safety, including rare events such as severe hypoglycemia and development of preeclampsia, are also needed.

The EVOLVE cohort study aimed to evaluate the risk of having offspring with major congenital malformations or perinatal or neonatal death, when using detemir versus other basal insulins, in pregnant women with preexisting diabetes. It also set out to examine other important maternal end points, including HbA_{1c} levels during pregnancy and the incidence of major hypoglycemia and preeclampsia.

RESEARCH DESIGN AND METHODS

The EVOLVE study design has been published previously (25). In brief, the EVOLVE study (ClinicalTrials.gov, NCT01892319) was a large, multinational, prospective, noninterventional, multicenter study in pregnant women with preexisting type 1 or type 2 diabetes designed, in collaboration with the EMA, to assess the safety of detemir compared with other basal insulins during pregnancy. Women were enrolled in early pregnancy across 92 sites in 17 countries (including Europe, Israel, and Malaysia) (Table 1). Baseline data covering the prepregnancy period were collected at enrollment, after which the participants underwent a series of standard routine visits throughout pregnancy (frequency determined by the study site and data collected in the context of routine practice), up until delivery. After delivery, there was a 1-month follow-up (or within a month of the delivery date) and an additional 1-year follow-up (within 4 months of the 1-year follow-up date). Postpartum follow-up was performed using questionnaires and telephone interviews (25).

Participants were required to have a positive pregnancy test (gestational age $\leq$16 weeks at enrollment), type 1 or type 2 diabetes diagnosed prior to conception (no gestational diabetes), treatment at the time of enrollment with detemir or other injectable antidiabetic treatments, and unchanged basal insulin type or other injectable antidiabetic treatment products from 4 weeks prior to conception until study enrollment. For the results presented in this study, only women treated with detemir and other basal insulins and who did not change the type of basal insulin during early pregnancy were included. Women could participate in the study more than once. Recruitment took place between September 2013 and September 2018, and informed consent was given.

End Points

The primary end point was a composite of the proportion of pregnancies completing $\geq$22 weeks of gestation in women treated with detemir versus other basal insulins, without any of the following

Table 1—Baseline characteristics and glucose-lowering treatment of pregnant women with preexisting diabetes using detemir vs. other basal insulins at enrollment

	Detemir (n = 727)	Other basal insulins (n = 730)
Country, *n* (%)		
Croatia	238 (32.7)	47 (6.4)
Denmark	126 (17.3)	257 (35.2)
Finland	57 (7.8)	50 (6.8)
France	9 (1.2)	15 (2.1)
Germany	4 (0.6)	9 (1.2)
Greece	4 (0.6)	7 (1.0)
Ireland	28 (3.9)	31 (4.2)
Israel	53 (7.3)	8 (1.1)
Italy	15 (2.1)	21 (2.9)
Malaysia	5 (0.7)	14 (1.9)
The Netherlands	11 (1.5)	6 (0.8)
Norway	4 (0.6)	20 (2.7)
Poland	19 (2.6)	38 (5.2)
Portugal	3 (0.4)	12 (1.6)
Romania	22 (3.0)	1 (0.1)
Spain	27 (3.7)	87 (11.9)
U.K.	102 (14.0)	107 (14.7)
Type 1 diabetes, *n* (%)	595 (81.8)	654 (89.6)
Type 2 diabetes, *n* (%)	132 (18.2)	76 (10.4)
Age, years, mean (SD)	31.1 (5.1)	30.6 (5.3)
BMI, kg/m^2, mean (SD)	25.8 (5.7)	26.6 (5.7)
Systolic blood pressure, mmHg, mean (SD)	117.4 (13.5)	119.5 (13.9)
Diabetes duration, years, mean (SD)	13.1 (8.1)	13.6 (8.5)
History of retinopathy, *n* (%)	155 (21.4)	158 (21.9)
History of nephropathy, *n* (%)	34 (4.7)	30 (4.1)
Hypertension, *n* (%)	64 (8.8)	60 (8.2)
HbA_{1c}, % [mmol/mol], mean (SD)	7.0 (1.3) [53 (14)]	7.2 (1.4) [55 (15)]
White, *n* (%)	688 (96.0)	649 (90.8)
University degree, *n* (%)	203 (30.2)	154 (23.2)
Current smoker, *n* (%)	66 (9.3)	67 (9.5)
Alcohol consumption, *n* (%)	7 (1.0)	8 (1.2)
Gestational age of current pregnancy at enrollment, weeks, mean (SD)	8.7 (2.5)	8.8 (2.6)
Folic acid taken before and during first trimester, *n* (%)	459 (63.9)	579 (80.1)
Number of previous pregnancies, *n* (%)		
0	229 (31.5)	260 (35.6)
1	268 (36.9)	247 (33.8)
2	114 (15.7)	116 (15.9)
3	59 (8.1)	58 (7.9)
≥4	57 (7.8)	49 (6.7)
Number of previous live births, *n* (%)		
0	325 (46.0)	290 (43.9)
1	283 (40.1)	276 (41.8)
2	74 (10.5)	77 (11.6)
3	13 (1.8)	17 (2.6)
≥4	11 (1.6)	1 (0.2)
Previous pregnancy complications, *n* (%)	375 (54.0)	351 (54.0)
Previous preeclampsia, *n* (%)	28 (3.9)	32 (4.4)
Previous perinatal deaths, *n* (%)	13 (1.8)	12 (1.6)

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events: major congenital malformations, perinatal death (from 22 weeks before to 7 days after birth), or neonatal death (death of a liveborn infant from 0 to 28 days after delivery). A major congenital malformation was defined as a life-threatening structural anomaly or an abnormality likely to cause significant impairment of health or functional capacity and that needs medical or surgical treatment (26). The number of pregnancies resulting in abortions, stillbirth (from 22 weeks and until birth), perinatal death, or neonatal death was determined. The number of fetuses with major and/or minor congenital malformations was also assessed, in which minor malformation was defined as not fulfilling the criteria for major malformation.

Maternal end points included HbA_{1c} levels and safety end points, namely the incidence of major hypoglycemia and preeclampsia during pregnancy. Major hypoglycemia was defined as a hypoglycemic episode in which the patient is not able to treat herself and oral carbohydrates, glucagon, or intravenous glucose must be administered to the patient by another person because of severe central nervous system dysfunction.

Statistical Methods

All statistical tests were performed as two-sided tests with a significance level of 0.05, and all statistical analyses were performed for all countries combined. In case of missing information on required variables, patients were excluded from respective analyses. For all binary end points (yes/no), *n* and percent were reported for the detemir group and for the "other basal insulins" group and the absolute risk difference between these proportions calculated, along with the 95% CI and the *P* value.

For all primary and secondary end points, both crude and confounder-adjusted analyses were performed. Potential confounding was adjusted for by propensity score matching (binary end points, using the Newcombe Method [27] or multiple regression analysis [continuous end points (HbA_{1c})]).

The primary end point was adjusted for country, maternal age, gestational age, diabetes type, duration of diabetes, history of any diabetes complications (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, or macrovascular

Table 1—Continued

	Detemir (n = 727)	Other basal insulins (n = 730)
Previous preterm delivery, *n* (%)	47 (6.5)	55 (7.5)
Previous spontaneous abortion, *n* (%)	185 (25.4)	162 (22.2)
Previous cesarean section, *n* (%)	172 (23.7)	119 (16.3)
Previous major malformations, *n* (%)	12 (1.7)	9 (1.2)
Previous minor malformations, *n* (%)	2 (0.3)	6 (0.8)
Glucose-lowering treatment, *n* (%)		
Basal insulin	727 (100)	730 (100)
Detemir	727 (100)	—
Insulin glargine	—	594 (81.4)
NPH insulin	—	95 (13.0)
Insulin degludec	—	40 (5.5)
Unknown type	—	1 (0.1)
Bolus insulin	714 (98.2)	713 (97.7)
Insulin aspart	605 (83.2)	530 (72.6)
Insulin lispro	92 (12.7)	120 (16.4)
Insulin glulisine	11 (1.5)	39 (5.3)
Regular human insulin	5 (0.7)	22 (3.0)
Unknown type	1 (0.1)	2 (0.0)
Metformin	36 (5.0)	32 (4.4)

Data for other concomitant diseases not shown.

complications), history of hypertension, folic acid taken before and during the first trimester, history of spontaneous abortion, history of cesarean section, history of preterm delivery, history of major malformations, number of previous pregnancies, BMI, HbA_{1c}, tobacco and alcohol consumption, and education.

Descriptive statistics of observed HbA_{1c} around conception, end of first trimester, end of second trimester, and end of third trimester were reported. The association between treatment group at enrollment and HbA_{1c} during pregnancy was examined by a linear mixed model for repeated measurements. An unstructured covariance matrix was used, and both crude and adjusted models were evaluated. Women were included as random effects to adjust for within-women clustering, and fixed factors of country, age, gestational week, type of diabetes, diabetes duration, history of diabetes complications, history of fetal pregnancy complications, BMI, tobacco and alcohol consumption, education, and bolus insulin and oral antidiabetic drug use were included. An interaction term between time and basal insulin treatment group was also evaluated to test (type 3 test) for differences in development of HbA_{1c} over time. Differences in HbA_{1c} between basal insulin treatment groups were estimated around conception and at the end of the first, second and third trimesters. The OBSMARGINS option, in the SAS/STAT 14.2 software PROC MIXED LSMEANS statement, was used when estimating mean HbA_{1c} during pregnancy, to ensure that estimates were weighted to represent the original sample and not an artificially balanced sample. Similar analyses as described for the primary end point were performed for the secondary safety end points (major hypoglycemia or preeclampsia during pregnancy, perinatal death, neonatal death, stillbirth, induced abortion due to major malformation, spontaneous abortion, and major or minor congenital malformations).

Ethics Statement

All participants gave their written informed consent to participate in this observational cohort study. This study was conducted in accordance with International Society for Pharmaceutical Engineering guidelines for Good Pharmacoepidemiology Practice and the Declaration of Helsinki and was approved separately in each of the participating countries by national health authorities, local institutional review boards, or independent ethics committees.

RESULTS

Overall, 2,373 women met the inclusion criteria for the study and, of these, 1,457 were receiving basal insulin at enrollment and were treated with unchanged basal insulin type during early pregnancy. Women who changed type of basal insulin during pregnancy (135) or who were not receiving basal insulin at enrollment, likely due to pump treatment (781), were not included in this analysis (Fig. 1). In total, 727 women were using insulin detemir as a basal insulin, and 730 women were using other basal insulins (Fig. 1). One woman on other basal insulin withdrew from the study prior to pregnancy termination. The remaining 1,456 mothers included in the study were pregnant with 1,431 singletons and 25 twin pairs (1,481 fetuses), 713 singletons and 14 twin pairs (741 fetuses) in the 727 mothers receiving detemir, and 718 singletons and 11 twin pairs (740 fetuses) in the 729 mothers on other basal insulins (Fig. 1). Of 1,481 fetuses, 1,360 were born (≥22 gestational weeks), with 1,345 being liveborn (Fig. 1).

Baseline characteristics of the women included in the study were comparable between treatment groups, with a few differences (Table 1). The majority of participants (detemir, 81.8%; other basal insulins, 89.6%) had type 1 diabetes. A lower percentage (63.9%) of women using detemir had folic acid supplementation before and/or during the first trimester than those using other basal insulins (80.1%). Of those using other basal insulins at enrollment, 81.4% were using insulin glargine. In both treatment groups, the majority of participants were using insulin aspart as bolus insulin (detemir group, 83.2%; other basal insulin group, 72.6%).

The unadjusted prevalence of newborns without major congenital malformations, perinatal or neonatal death was similar between detemir (97.0% [n = 647/667]) and other basal insulins (95.5% [n = 633/663]) (crude risk difference 0.015 [95% CI −0.01, 0.04], P = 0.1518; adjusted risk difference −0.003 [95% CI −0.03, 0.03], P = 0.8575).

The crude prevalence of a fetus with at least one major or minor congenital malformation was lower with detemir versus other basal insulins (9.4% vs. 12.6%), as was the case for the prevalence of at least one major congenital fetal malformation (2.7% vs. 3.8%) or at

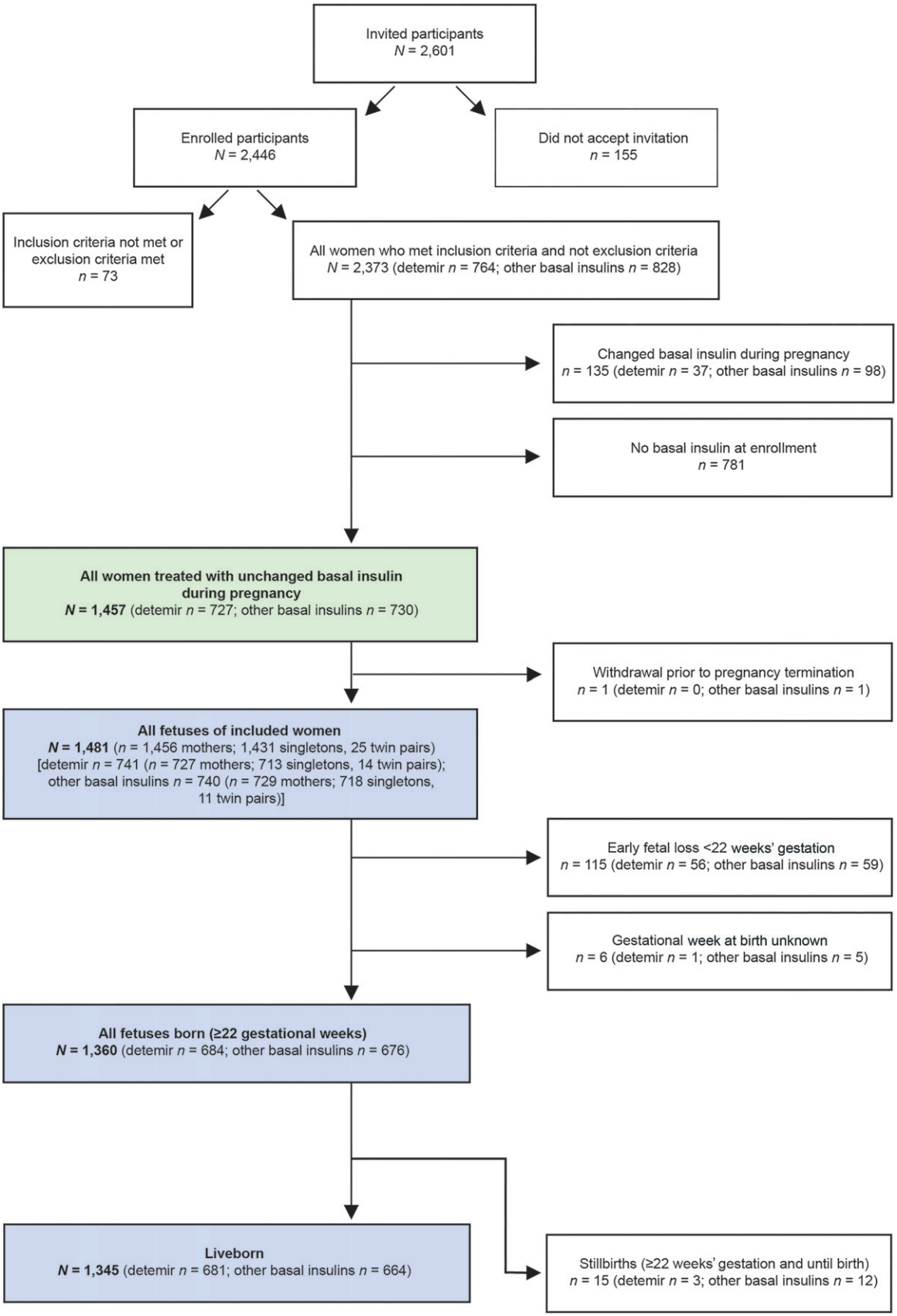

Figure 1—Patient disposition. *N*, number of cases.

least one minor malformation (6.7% vs. 8.7%). However, differences were not significant, either before or after adjustment for confounders (Fig. 2).

A total of 20 fetuses had at least one major congenital malformation in the detemir group versus 28 in the other basal insulin group. The most common major congenital malformations were related to the cardiovascular system (10 reported in the detemir group vs. 9 with other basal insulins), the genitourinary system (4 vs. 9), and the nervous system (7 vs. 8). A total of 49 fetuses in the detemir group had at least one minor, but no major, congenital malformations, versus 64 in the other basal insulin group. The most common minor congenital malformation was also related to the cardiovascular system (16 vs. 29 reported), followed by the genitourinary system (16 vs. 13).

The crude prevalence of perinatal death was lower with detemir versus other basal insulins (0.9% vs. 1.9%), as was the case for stillbirth (0.4% vs. 1.8%) or induced abortion of fetuses with major congenital malformations (0.7% vs. 1.2%) (Fig. 2). Although this difference was significant for stillbirth prior to adjustment, differences were not significant for any of these variables following adjustment for confounders (Fig. 2).

Estimated mean maternal HbA_{1c} levels during pregnancy gradually decreased from conception (7.3% [56 mmol/mol] in patients using detemir and 7.5% [58 mmol/mol] with other basal insulins) to the end of the first (6.5% [48 mmol/mol] and 6.7% [50 mmol/mol]) and second trimesters (6.1% [43 mmol/mol] and 6.3% [45 mmol/mol]), after which levels rose slightly again at the end of the third trimester (6.3% [45 mmol/mol] and 6.4% [46 mmol/mol]) (Table 2). The crude estimated mean difference was significant at the end of the first (−0.181 [95% CI (−0.300, −0.062]; $P = 0.003$) and second (−0.139; [95% CI −0.232, −0.046]; $P = 0.003$) trimesters. However, no significant difference in estimated means was observed after adjustment for confounders (first trimester −0.070 [95% CI −0.201, 0.061]; and second trimester −0.013 [95% CI −0.121, 0.094]).

The crude analysis showed a significantly lower risk of major hypoglycemia (6.0% vs. 9.0%) and preeclampsia (6.4% vs. 10.0%) during pregnancy in women using detemir compared with other basal

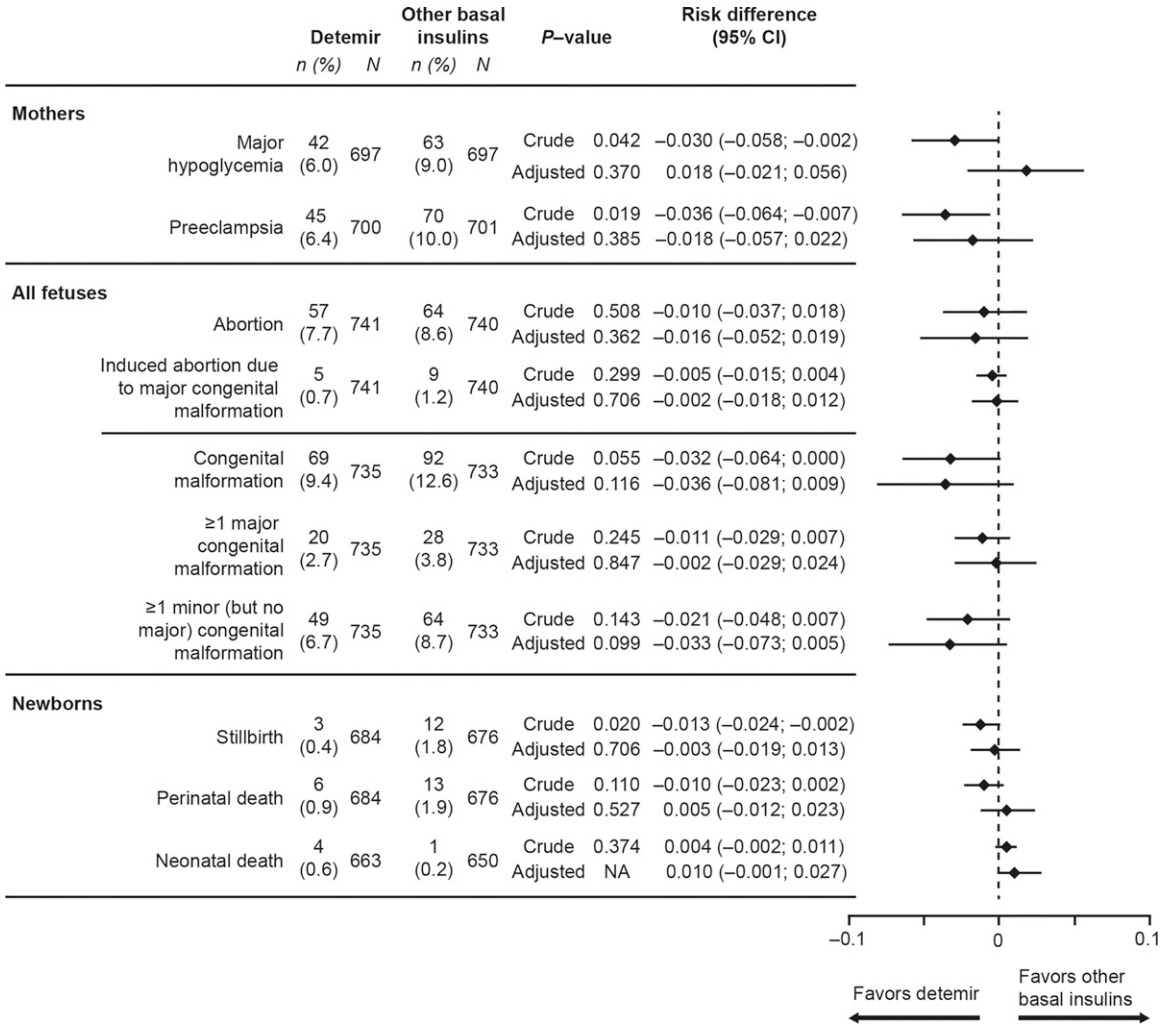

Figure 2—Secondary pregnancy outcomes using detemir vs. other basal insulin, Absolute numbers shown for data before propensity score matching (crude data). Total *n* in analyses differs due to missing information on some of the end points. Adjusted values were adjusted by propensity score matching. NA, not available.

Table 2—Maternal HbA_{1c} with detemir vs. other basal insulin

	Detemir	Other basal insulins		
	All mothers (n = 727)	All mothers (n = 730)	Crude mean difference (95% CI),* P value	Adjusted mean difference (95% CI),* P value
Estimated mean HbA_{1c}, % (mmol/mol)				
Around conception	7.3 (56)	7.5 (58)	−0.145 (−0.350, 0.059), 0.163	−0.051 (−0.280, 0.178), 0.665
End of first trimester	6.5 (48)	6.7 (50)	−0.181 (−0.300, −0.062), 0.003	−0.070 (−0.201, 0.061), 0.296
End of second trimester	6.1 (43)	6.3 (45)	−0.139 (−0.232, −0.046), 0.003	−0.013 (−0.121, 0.094), 0.805
End of third trimester	6.3 (45)	6.4 (46)	−0.085 (−0.184, 0.014), 0.093	0.015 (−0.101, 0.132), 0.796

The association between treatment group and HbA_{1c} during pregnancy was examined by a linear mixed model for repeated measurements. An unstructured covariance matrix was used. Estimated mean HbA_{1c} values are shown for crude data. Women were included as random effects to adjust for within-women clustering, and fixed factors of country, age, gestational week, type of diabetes, diabetes duration, history of diabetes complications, history of severe hypoglycemia, history of fetal pregnancy complications, BMI, tobacco use, alcohol consumption, education, and bolus insulin and oral antidiabetic drug use were included. An interaction term between time and basal insulin treatment group was also evaluated to test (type 3 test) for differences in development of HbA_{1c} over time. The OBSMARGINS option was used when estimating mean HbA_{1c}. *Expressed in units of percent.

insulins (Fig. 2). However, these differences were no longer significant following adjustment for confounders (Fig. 2).

CONCLUSIONS

EVOLVE was a large prospective observational study evaluating the incidence of severe pregnancy complications in women with preexisting diabetes treated with detemir or other basal insulins in a real-world setting. The chance of having a newborn without major congenital malformations or perinatal or neonatal death was comparable between insulin detemir and other basal insulins. Crude analysis demonstrated a lower level of HbA_{1c} and lower prevalence of major hypoglycemia, preeclampsia, and stillbirth in women using detemir, but these differences did not persist after adjustments.

Evidence for the effective use of basal insulin analogs in pregnant women with diabetes has largely come from retrospective studies (20,28,29). A large population-based cohort study, which included 1,661 women with pregestational diabetes from seven European regions, has previously demonstrated a lower risk of major congenital malformations when using insulin analogs compared with human insulin (30). Our previously published RCT investigated the use of detemir versus NPH insulin, both in combination with insulin aspart, in 310 pregnant women with type 1 diabetes (22). Data presented in the current prospective real-world cohort expand the data set more than fourfold and are in agreement with the low risk of these pregnancy complications previously seen with detemir in the randomized clinical trial (22,23). Despite the difference in the number of congenital malformations in women using detemir compared with other basal insulins not being statistically significant, the findings presented in this study may still be of clinical importance. Further studies evaluating the occurrence of congenital malformations with different insulin treatments are warranted.

Data from this large, prospective, observational cohort provide further support for the HbA_{1c}-lowering effect of detemir in pregnant women with preexisting diabetes. The current study has a number of strengths. It was designed in collaboration with the EMA and used real-world data with a large sample size, covering many nationalities, ethnicities, and health systems. Longitudinal data were collected prospectively, in the context of routine practice, from early pregnancy to the age of 1 year of the infant. Inclusion criteria were broad, with very few exclusion criteria, and hence the results should be more broadly applicable to the real-world population than those of typical RCTs. Finally, there were many covariates for confounder control. Study limitations included the fact that real-life studies are not as strictly controlled as RCTs, women were recruited at selected specialized diabetes sites, and adverse pregnancy outcomes very early in pregnancy may have been missed. There were, in general, few events, due to their rarity, that resulted in relatively low statistical power for some end points. It is also important to stress that the number of women and fetuses included in the adjusted analysis were reduced considerably (by ∼40%) after propensity score matching.

To prevent congenital malformations, such as neural tube defects (31), women are advised to take folic acid supplementation prior to conception and in early pregnancy (32–34). Folic acid intake was unlikely to be a contributor to the numerically lower number of congenital malformations seen among women using insulin detemir since the intake of folic acid was reported to be less frequent in the insulin detemir group.

The prevalence of other chronic diseases and medication that may have an impact on the development of congenital malformations (35–43), as well as late diabetic complications such as diabetic nephropathy (44), were similar in the two treatment groups. HbA_{1c} during the first trimester and the prevalence of major hypoglycemia were lower in women using insulin detemir in the crude analysis, and whether this might contribute to the numerically lower numbers of congenital malformations remains speculative. The majority of patients included in EVOLVE had type 1 diabetes. However, the pathophysiology of increased prevalence of congenital malformations and perinatal death in women with diabetes is linked to elevated blood glucose and is therefore likely to be similar in type 1 and type 2 diabetes (6).

Stillbirths were less common in women using insulin detemir. Whether a lower HbA_{1c} value during the development of the placenta, and a more stable fasting glucose, with insulin detemir in

comparison with other basal insulins throughout pregnancy play a role in this finding remain speculative (7).

Several important clinical outcomes (i.e., lower HbA_{1c} and lower prevalence of severe hypoglycemia, preeclampsia, and stillbirth, as well as a numerically lower number of congenital malformations) in women using detemir were seen in the crude analysis. These differences did not persist after adjustments, but the number of women and fetuses included in the adjusted analysis were reduced considerably after propensity score matching. Even larger studies are needed to make firm conclusions.

In conclusion, treatment with insulin detemir was associated with a comparable risk to other basal insulins of major congenital malformations, perinatal or neonatal death, hypoglycemia, preeclampsia, and stillbirth.

Acknowledgments. The authors thank all investigators, staff, and participants of this study. The authors also thank Rikke Baastrup Nordsborg and Usha Thamattoor for data analysis, Charlotte Højelse for study management, and Pranav Kelkar and Renuka Munikrishnappa, all from Novo Nordisk, for the input into the manuscript. Medical writing and editorial assistance were provided by Jane Blackburn, Amy Hepple, and Helen Marshall of Ashfield MedComms, an Ashfield Health company, funded by Novo Nordisk A/S. A complete list of the investigators in the EVOLVE study can be found in the Supplementary Material.

Funding. The EVOLVE study, including study design, data collection, analysis, and interpretation, was funded by Novo Nordisk A/S. Medical writing and editorial assistance were also sponsored by Novo Nordisk A/S.

Duality of Interest. E.R.M. has received speakers fees from Novo Nordisk, Eli Lilly and Company, and Sanofi Aventis; has participated in steering committee tasks and guidance involving writing protocols for Novo Nordisk; is participating in several multinational clinical studies on the use of insulin in pregnant women with preexisting diabetes, in collaboration with Novo Nordisk. K.C. has received speaker honoraria from or has participated in advisory boards for Novo Nordisk, Eli Lilly and Company, Sanofi, AstraZeneca, Boehringer Ingelheim, and Servier. J.D. has received speaker honoraria from or has participated in advisory boards for Novo Nordisk, Eli Lilly and Company, Sanofi, Amgen, Abbott, AstraZeneca, Boehringer Ingelheim, Mundipharma, and Merck Sharp & Dohme. A.C.A., M.-A.G., and L.L.N.H. are employees of, and hold shares in, Novo Nordisk. S.D.G. is a consultant for Sanofi, Eli Lilly and Company, Novo Nordisk, Takeda Pharmaceutical Company, Merck Sharp & Dohme, Servier, and Theracos. H.P.H. has received lecturer and scientific advisor fees from Abbott, AstraZeneca, Eli Lilly and Company, Insulet, LifeScan, and Novo Nordisk and research grants from Abbott, LifeScan, and Novo Nordisk. H.-P.K. has received speaker honoraria from, or has participated in advisory boards for, Novo Nordisk, Eli Lilly and Company, Sanofi, AstraZeneca, and Servier. D.R.M. has received speaker honoraria from, or has participated in advisory boards for, Novo Nordisk. P.D. is participating in clinical studies on the use of insulin analogs in pregnant women with preexisting diabetes and participates in an expert committee on this topic, in collaboration with Novo Nordisk, no personal honorarium is involved. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. E.R.M., N.A., A.C.A., E.A., K.C., H.d.V., J.D., F.D., M.-A.G., S.D.G., H.P.H., L.L.N.H., M.I., H.-P.K., D.R.M., and P.D. all interpreted results and provided input, critical review, and approval for the manuscript. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. E.R.M. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This work was presented in poster form at the 80th Scientific Sessions of the American Diabetes Association, 12–16 June 2020, and in oral form at the 56th Annual Meeting of the European Association for the Study of Diabetes, 21–25 September 2020.

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