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Original article

Determinants of a good perinatal outcome in 588 pregnancies in women with type 1 diabetes

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ABSTRACT

Aim. – This study assessed pregnancy outcomes in women with type 1 diabetes (T1D) over the last 15 years and identified modifiable factors associated with good perinatal outcomes.
Methods. – Pregnancy outcomes were prospectively assessed in this cohort study of 588 singleton pregnancies (441 women) managed by standardized care from 2000 to 2014. A good perinatal outcome was defined as the uncomplicated delivery of a normally formed, non-macrosomic, full-term infant with no neonatal morbidity. Factors associated with good perinatal outcomes were identified by logistic regression.
Results. – The rate of severe congenital malformations was 1.5%, and 0.7% for perinatal mortality. The most frequent perinatal complications were macrosomia (41%), preterm delivery (16%) and neonatal hypoglycaemia (11%). Shoulder dystocia occurred in 2.6% of cases, but without sequelae. Perinatal outcomes were good in 254 (44%) pregnancies, and were associated with lower maternal HbA_{1c} values at delivery [adjusted odds ratio (aOR): 2.78, 95% CI: 2.04–3.70, for each 1% (11 mmol/mol) absolute decrease], lower gestational weight gains (aOR: 1.06, 95% CI: 1.02–1.10) and absence of preeclampsia (aOR: 2.63, 95% CI: 1.09–6.25). The relationship between HbA_{1c} at delivery and a good perinatal outcome was continuous, with no discrimination threshold.
Conclusion. – In our study, rates of severe congenital malformations and perinatal mortality were similar to those of the general population. Less severe complications, mainly macrosomia and late preterm delivery, persisted. Also, our study identified modifiable risk factors that could be targeted to further improve the prognosis of pregnancy in T1D.

Introduction

In 1989, the St Vincent Declaration set the healthcare goal that outcomes of pregnancies in women with diabetes should approximate those of the background population [1]. Yet, a recent review of 12 studies comparing women with type 1 diabetes (T1D) with background populations still reported higher rates of congenital malformations [5.0% *vs* 2.1%, relative risk (RR): 2.4], perinatal mortality (2.7% *vs* 0.72%, RR: 3.7), preterm delivery (25.2% *vs* 6.0%, RR: 4.2) and large-for-gestational-age (LGA) infants (54.2% *vs* 10.0%, RR: 4.5) [2]. A cross-sectional study performed in 12 French reference centres during 2000–2001 yielded similar results [3].

Maternal hyperglycaemia was a major risk factor for these adverse outcomes. Indeed, the rate of congenital malformations increased linearly with HbA_{1c} levels > 6.3% [4], leading to recommendations for preconception HbA_{1c} targets < 6.5% [5] or < 6.1% [6]. In addition, greater risks of stillbirth and emergency caesarean delivery for fetal compromise have also been associated with levels of HbA_{1c} > 7.5% in late pregnancy [7] and $HbA_{1c} \geq 6.4\%$ at delivery [8], while the rate of perinatal death in normally formed offspring is increased linearly with periconceptional HbA_{1c} values > 6.6% [9].

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As for other perinatal outcomes, HbA_{1c} targets and the stages of pregnancy at which they have to be achieved have not been consistently identified. For example, an increased risk of preterm delivery has been associated with third-trimester HbA_{1c} levels in some studies [10,11], but with first-trimester levels in others [12]. Similarly, the rate of macrosomia has been associated with HbA_{1c} values during the second and third trimesters in some studies [12–16], while others suggest an association as early as the first trimester [17,18]. Moreover, besides blood glucose control, an increased risk of adverse perinatal outcomes has been associated with a number of factors, including lack of preconception care, low socioeconomic status, smoking, high prepregnancy body mass index (BMI), excessive gestational weight gain and presence of diabetic nephropathy. Thus, our present study aims were to assess pregnancy outcomes in a cohort of women with T1D over the last 15 years and to identify modifiable factors associated with good perinatal outcomes.

Materials and methods

All women with T1D and an evolving singleton pregnancy followed in the Department of Obstetrics, Cochin–Saint Vincent de Paul Hospital, from 2000 to 2014 (442 women, 588 pregnancies) were consecutively included in the present cohort study, which was approved by the institutional review board (Comité de protection des personnes se prêtant à la recherche biomédicale Île-de-France 3). Preconception care, management of diabetes during pregnancy, and obstetric follow-up and management were standardized as previously described [8,10]. Briefly, preconception care included assessment of diabetes complications, and optimization of diet and of insulin therapy, delivered by four daily injections or by continuous subcutaneous insulin infusion (CSII), using an external insulin pump, with capillary blood glucose self-monitoring before and 2 h after each meal, strict targets [< 95 mg/dL (5.3 mmol/L) and < 120 mg/dL (6.7 mmol/L), respectively], and supplementation with folic acid (5 mg/day).

During their pregnancies, women were seen every other week at the diabetes clinic and could contact a member of the team as often as necessary. HbA_{1c} was measured by high-performance liquid chromatography (normal 4–6%) at periconception, during the first and second trimesters, and at delivery. All women were followed monthly at the obstetric clinic and had three ultrasound scans (at 12–14, 22–24 and 32–34 weeks of gestation). Non-stress tests were performed twice weekly from 32 weeks until delivery. Timing of delivery was guided by gestational age: in the absence of complications, delivery was planned at 38 or 39 weeks of gestation; otherwise, when delivery was indicated for maternal or fetal reasons, it was decided after case-by-case risk–benefit assessment. The route of delivery was chosen based on obstetric conditions: caesarean delivery without labour was planned for fetal malpresentation (breech, transverse) or placenta praevia, and was encouraged for suspected fetal macrosomia. Suspicion of macrosomia was based on symphysis–fundal height measurements > 40 cm combined with Leopold's manoeuvres and/or fetal abdominal circumferences $>$ 97th percentile on ultrasonography performed a week before delivery. A trial of labour was attempted in women with cephalic presentations, normal placental insertions and no suspected macrosomia. In women with previous caesarean deliveries, the decision to attempt vaginal birth was made on a case-by-case basis [19].

Maternal characteristics were prospectively collected and included age, ethnicity, socioeconomic status, parity, smoking habit, prepregnancy BMI, diabetes duration, presence of retinopathy, nephropathy or chronic hypertension (defined as hypertension prior to pregnancy or diagnosed before week 20 of gestation), preconception care, supplementation with folic acid, treatment by CSII, gestational weight gain and HbA_{1c} values.

Maternal, fetal and perinatal outcomes were assessed over three 5-year periods (2000–2004, 2005–2009 and 2010–2014). Maternal outcomes included preeclampsia, defined according to the US National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [20], and mode of delivery [caesarean (elective or emergency) *vs* vaginal delivery].

Fetal and perinatal adverse outcomes included: major congenital malformations, classified according to EUROCAT [21]; termination of pregnancy; delivery of an LGA infant, defined as a birth weight $\geq$ 90th percentile according to French growth standards [22]; perinatal death (stillbirth after 22 weeks of gestation or neonatal death within the first 28 days of life); preterm delivery, defined as delivery before 37 weeks of gestation; shoulder dystocia, defined as delivery requiring additional obstetric manoeuvres following failure of gentle downward traction on the fetal head to effect delivery of the shoulders; birth trauma (bone fracture, brachial plexus injury); admission to the neonatal intensive care unit (NICU); neonatal hypoglycaemia, defined as a 1- to 3-h plasma glucose level < 40 mg/dL (2.2 mmol/L); and respiratory distress syndrome, defined as the need for oxygen therapy or invasive ventilation for > 24 h. Hyperbilirubinaemia requiring phototherapy was not recorded.

The primary outcome was a good perinatal outcome, defined as the uncomplicated delivery of a normally formed, non-LGA infant after either spontaneous labour at ≥ 37 weeks of gestation or induction of labour at ≥ 38 weeks of gestation, with no perinatal complications. An adverse perinatal outcome was defined as the occurrence of any of the above-mentioned complications. Analysis of perinatal outcomes was performed after the exclusion of six pregnancies considered non-evolutive: four were terminations because of major congenital malformations; one was fetal loss at 17 weeks of gestation; and one was neonatal death due to anencephaly (the mother declined pregnancy termination), leaving 582 pregnancies.

As macrosomia and preterm delivery are the two most frequent adverse outcomes of pregnancy in women with T1D [23], two secondary outcomes were also analyzed: deliveries of infants without macrosomia; and deliveries of full-term infants.

Comparisons between groups were made using non-parametric tests (Mann–Whitney, Kruskal–Wallis and Dunn's) for multiple comparisons. Categorical variables were compared using Fisher's exact test. Factors associated with good perinatal outcomes on univariable analyses with a P-value < 0.10 were entered into the multivariable analyses. In cases of collinearity between two or more variables, the most clinically pertinent one was chosen. Factors independently associated with perinatal outcomes were assessed by logistic regression. Adjusted odds ratios (aORs) are reported with their 95% confidence intervals (CI). Multilevel modelling was performed to take into account the clustering effect of women who had several pregnancies.

Because HbA_{1c} levels have been associated with pregnancy outcomes in women with T1D, receiver-operating characteristic (ROC) curve analyses were also performed to search for the HbA_{1c} thresholds (preconception, during the first and second trimesters, and at delivery) predictive of good perinatal outcomes. Statistical analyses were performed using Stata 11.0 software (StataCorp LP, College Station, TX, USA).

Results

Over the 15-year study period, our department consecutively managed 588 singleton pregnancies in 441 women with T1D. In this series, 322 women delivered once, 95 twice, 21 three times, two four times and one five times. The main characteristics of these

women and their pregnancies by study period are presented in Table 1. For the entire cohort, periconceptional HbA_{1c} was 6.8% (6.3–7.5%); otherwise, it was < 6.5% and < 6.0% in 31% and 15% of women, respectively, and at delivery, < 6.5% and < 6.0% in 70% and 41% of women, respectively.

Congenital malformations, including two chromosomal abnormalities, were found in nine cases (1.5%), and led to early termination of pregnancy in four women. The rate of perinatal death was 0.7% (4/588). There were two stillbirths: in one case, the pregnancy was unplanned, periconceptional HbA_{1c} was 8.1% and stillbirth occurred at 35 weeks of gestation, with an HbA_{1c} of 7.7% at delivery; the other case happened at 37.5 weeks of gestation, the pregnancy was planned, and the periconceptional HbA_{1c} was 7.0% and 6.3% at delivery. No definite cause of stillbirth was identified in either case. There were also two neonatal deaths. In one case, the mother was taking valproate treatment and her periconceptional HbA_{1c} was 7.8%; anencephaly was diagnosed but termination of pregnancy was declined, and the infant died soon after delivery at 37 weeks of gestation. The second case involved a non-malformed fetus that died soon after an emergency caesarean delivery because of an abnormal non-stress test at 37 weeks of gestation.

Otherwise, good perinatal outcomes were observed in 254 pregnancies (44%). Adverse outcomes (which may have been related to each other) were noted in 328 cases, including: the two above-mentioned perinatal deaths; 93 preterm births (16%); 15 cases of shoulder dystocia (2.6%); three bone fractures (0.5%); two transient cases of brachial plexus injury (0.3%); one antenatal intracerebral haemorrhage; 238 births of a LGA infant (41%); 110 NICU admissions (19%); 64 cases of neonatal hypoglycaemia (11%); and 14 cases of respiratory distress syndrome (2.4%).

The perinatal outcomes for all 582 pregnancies according to study period are shown in Table S1 (see supplementary materials associated with this article online). Median gestational age at delivery was the same for all three-study periods, although the distribution of gestational age was significantly skewed towards higher values in the last 5 years ($P < 10^{-4}$ by analysis of variance; $P < 0.01$ for the last *vs* both first and second periods). There was no significant change in rates of preterm deliveries, whereas the rate of LGA infants decreased, as did the rate of caesarean deliveries. Although rates of shoulder dystocia increased, the frequency of birth trauma remained low, and no sequelae were observed in the affected infants. The rate of neonatal hypoglycaemia decreased.

The main characteristics of our 582 pregnancies according to good *vs* adverse perinatal outcomes are presented in Table 2. On univariable analyses, nulliparity, lower prepregnancy BMI, absence of preeclampsia, and lower HbA_{1c} values at conception and throughout the pregnancy were significantly associated with good perinatal outcomes. In addition, HbA_{1c} values were available for 570 (98%) pregnancies at periconception, 566 (97%) during the first trimester, 549 (94%) during the second trimester and 562 (97%) at delivery. Strong correlations were observed between HbA_{1c} values at preconception, during the first and second trimesters, and at delivery ($P < 10^{-4}$ for all correlations). However, no significant improvement of HbA_{1c} values was observed during these pregnancies throughout the study period. On multivariable analyses, lower gestational weight gain, absence of preeclampsia, lower HbA_{1c} at delivery and delivery during the most recent time period were all independently associated with good perinatal outcomes (Table 3).

In the final model, HbA_{1c} at delivery was associated with a good perinatal outcome, with an aOR of 2.78 (95% CI: 2.04–3.70) for each 1% decrease in HbA_{1c}. A continuous relationship between HbA_{1c} at delivery and frequency of good perinatal outcome was also observed, with no identifiable threshold (Fig. 1). While a 6.0% HbA_{1c} level at delivery emerged as the best cut-off for predicting a good perinatal outcome by ROC analysis, the area under the curve (AUC), sensitivity and specificity were poor (0.632, 54.7% and 71.7%, respectively).

Factors associated with delivery of a non-macrosomic infant were assessed by multivariable analysis. Lower maternal age, nulliparity, smoking, lower prepregnancy BMI, presence of retinopathy and chronic arterial hypertension, lower gestational weight gain, lower HbA_{1c} at delivery and delivery during the most recent study period were all independently associated with delivery of an infant without macrosomia (Table S2; see supplementary materials associated with this article online).

In addition, factors associated with term delivery were also assessed by multivariable analysis. Older maternal age, treatment with CSII, absence of preeclampsia and lower HbA_{1c} at delivery remained independently associated with full-term delivery

Table 1
Main characteristics of women with type 1 diabetes at enrolment and during 588 pregnancies by study time period of delivery.

	2000–2004	2005–2009	2010–2014	*P*
Total women (*n*)	144	204	240	
Maternal age, years (*n*)	31 [28–34] (144)	32 [29–35] (204)	33 [29–36] (240)	0.0135
Euro-Caucasian: yes/no (%)	117/27 (81%)	130/74 (63.7%)	175/65 (72.9%)	0.0015
Low socioeconomic status: yes/no (%)	11/119 (8.5%)	14/181 (7.2%)	19/209 (8.3%)	0.8824
Nulliparous: yes/no (%)	78/66 (54%)	88/116 (43.1%)	96/144 (40%)	0.0227
Smoking: yes/no (%)	19/125 (13.2%)	24/180 (13.3%)	29/211 (12%)	0.9183
PP body mass index (BMI), kg/m^2 (*n*)	22.6 [21.2–24.9] (144)	23 [21.3–25.2] (204)	23.1 [21–25.1] (240)	0.7857
PP BMI: normal/overweight/obese (*n*)	108/28/8	148/44/12	168/57/15	0.8821
Diabetes duration, years (*n*)	14 [8–20] (143)	14 [8–20] (204)	15 [9–21] (237)	0.5810
Retinopathy: yes/no (%)	53/89 (37%)	74/129 (36.5%)	63/163 (28%)	0.0846
Nephropathy: yes/no (%)	17/125 (12%)	17/187 (8.3%)	14/219 (6%)	0.1270
Chronic hypertension: yes/no (%)	5/139 (3.5%)	8/196 (3.9%)	10/226 (4.2%)	0.9330
Preconception care: yes/no (%)	92/51 (64%)	116/88 (57%)	146/89 (62%)	0.3245
Preconception folic acid: yes/no (%)	48/79 (38%)	98/101 (49%)	127/104 (55%)	0.0079
Treatment with CSII: yes/no (%)	24/118 (16.9%)	57/146 (28%)	99/136 (42%)	$< 10^{-4}$
Gestational weight gain, kg (*n*)	12 [9–15] (139)	13 [10–16] (199)	13.5 [11–17] (239)	0.0017
Gestational hypertension: yes/no (%)	4/131 (3.0%)	9/179 (4.8%)	7/207 (3.3%)	0.6271
Preeclampsia: yes/no (%)	7/135 (4.9%)	12/188 (6.0%)	23/214 (9.7%)	0.1554
Periconceptional HbA_{1c}, % (*n*)	7.0 [6.4–7.6] (139)	6.8 [6.3–7.7] (199)	6.8 [6.2–7.4] (232)	0.2233
1st trimester HbA_{1c}, % (*n*)	6.6 [6.1–7.1] (138)	6.4 [5.9–6.9] (199)	6.4 [5.9–6.9] (229)	0.0559
2nd trimester HbA_{1c}, % (*n*)	6.1 [5.5–6.5] (129)	6.1 [5.6–6.5] (194)	6.1 [5.6–6.5] (226)	0.9360
HbA_{1c} at delivery, % (*n*)	6.0 [5.6–6.6] (138)	6.1 [5.8–6.5] (194)	6.0 [5.6–6.6] (230)	0.4661

Data are numbers (percentages) or medians [interquartile ranges] (number of cases). PP: prepregnancy; CSII: continuous subcutaneous insulin infusion (with an external pump).

Table 2
Factors associated with good *vs* adverse perinatal outcomes in 582 pregnancies in women with type 1 diabetes: univariable analysis.

	Good outcome ($n=254$)	Adverse outcome ($n=328$)	P
Maternal age, years	32 [28–35] (254)	32 [29–35] (328)	0.0626
Euro-Caucasian: yes/no (%)	188/66 (74)	231/97 (70)	0.4021
Low socioeconomic status: yes/no (%)	17/224 (7)	26/280 (8.5)	0.6318
Nulliparous: yes/no (%)	159/95 (63)	174/154 (53)	0.0227
Smoking: yes/no (%)	36/218 (14)	36/292 (11)	0.2556
PP body mass index (BMI), kg/m^2	22.8 [21–25] (254)	23.3 [21.4–25.4] (328)	0.0294
PP BMI: normal/overweight/obese	189/52/13	231/75/22	0.5242
Diabetes duration, years	13.5 [7–20] (253)	15 [8–21] (325)	0.0954
Retinopathy: yes/no (%)	81/164 (33)	107/213 (33)	1.000
Nephropathy: yes/no (%)	15/236 (6)	32/290 (10)	0.0932
Chronic hypertension: yes/no (%)	9/244 (3.5)	14/311 (4.3)	0.6754
Preconception care: yes/no (%)	157/95 (62)	194/130 (60)	0.6056
Preconception folic acid: yes/no (%)	124/119 (51)	146/162 (47)	0.4400
Treatment with CSII: yes/no (%)	88/165 (34.8)	90/231 (28)	0.0851
Gestational weight gain, kg	12 [10–16] (250)	13 [10–17] (318)	0.0715
Preeclampsia: yes/no (%)	7/246 (2.8)	35/291 (10.7)	0.0002
Periconceptional HbA_{1c}, % (n)	6.6 [6.0–7.3] (249)	7.0 [6.5–7.7] (321)	$<10^{-4}$
1st trimester HbA_{1c}, % (n)	6.3 [5.8–6.8] (246)	6.6 [6.2–7.1] (320)	$<10^{-4}$
2nd trimester HbA_{1c}, % (n)	5.9 [5.5–6.3] (240)	6.2 [5.8-6.7] (309)	$<10^{-4}$
HbA_{1c} at delivery, % (n)	5.9 [5.9–6.2] (244)	6.3 [5.9–6.8] (318)	$<10^{-4}$
Period of delivery			
2000–2004, n (%)	51 (20)	91 (28)	0.0838
2005–2009, n (%)	89 (35)	111 (34)	
2010–2014, n (%)	114 (45)	126 (38)	

Data are numbers (percentages), or medians [interquartile ranges] (number of cases); for definitions of good and adverse perinatal outcomes, see main text (Materials and Methods); PP: prepregnancy; CSII: continuous subcutaneous insulin infusion (with an external pump).

Table 3
Factors associated with good perinatal outcomes[a] in women with type 1 diabetes (547 pregnancies): multivariable analysis.

	P	aOR [95% CI]
Maternal age	0.053	1.04 [1.00–1.09]
Nulliparity: yes *vs* no	0.425	1.17 [0.79–1.74]
PP body mass index (BMI)	0.268	1.03 [0.98–1.09]
Diabetes duration	0.676	1.01 [0.98–1.03]
Treatment with CSII: yes *vs* no	0.122	1.37 [0.92–2.07]
Gestational weight gain	0.003	1.06 [1.02–1.10]
Preeclampsia: no *vs* yes	0.032	2.63 [1.09–6.25]
HbA_{1c} at delivery	<0.0001	2.78 [2.04–3.70]
Delivery during 2005–2009	0.013	1.88 [1.14–3.09]
Delivery during 2010–2014	0.002	2.21 [1.34–3.63]

Results are expressed as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). PP: prepregnancy; CSII: continuous subcutaneous insulin infusion.
[a] Defined as less gestational weight gain, no preeclampsia, lower HbA_{1c} at delivery and delivery during the most recent study years.

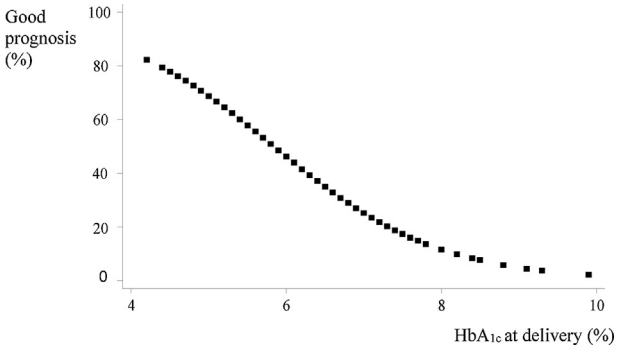

Fig. 1. Frequency of good perinatal outcomes according to HbA_{1c} values at delivery in 582 pregnancies in women with type 1 diabetes. Data are presented as percentages (black squares).

(Table S3; see supplementary materials associated with this article online).

Discussion

In our cohort of 588 pregnancies in women with T1D, the rates of severe congenital malformations (1.5%) and perinatal mortality (0.7%) were similar to those of the background population [21], and consistent with the results of a recent multicentre study performed in Ireland [24]. However, a recent nationwide study carried out in England and Wales reported persistently higher rates of congenital anomalies and neonatal death [25], which may have been related to the levels of preconceptional glycaemic control observed in that study: indeed, only 16% of women with T1D achieved periconceptional HbA_{1c} levels $<6.5\%$ compared with 31% in our present study.

In fact, our study showed that a good perinatal outcome, defined as the uncomplicated delivery of a normally formed, non-LGA, full-term infant with no neonatal morbidity, was achieved in only 44% of pregnancies. A significant decrease in the rate of caesarean sections was paralleled by a non-significant increase in shoulder dystocia, with no increase in the rate of birth trauma (Table S1).

The strengths of our real-life study were that all data were prospectively collected and outcomes recorded according to standard definitions. No eligible woman was excluded from the analysis; all were managed according to standardized protocols, none was lost to follow-up and multivariable analysis was performed to adjust for potential confounders. Limitations of the study were: its single-centre setting, which could limit extrapolation of our results; hyperbilirubinaemia requiring phototherapy, a recognized neonatal complication of infants born to women with T1D [23], was not recorded; and maternal hypoglycaemia was not systematically recorded, although no serious/maternal complications of hypoglycaemia were reported during the study periods.

Moreover, our study identified several potentially modifiable factors that may be targeted to improve perinatal outcomes in women with T1D, including gestational weight gain, preeclampsia and glycaemic control (Table 3). Excessive gestational weight gain is a known risk factor for macrosomia in T1D [26,27]. In our present study, lower gestational weight gain was independently associated with good perinatal outcomes and birth of a non-macrosomic

infant (Table 3, Table S2). Although the size of the effect was small in our cohort, interventions designed to limit excess gestational weight gain could help to reduce perinatal complications [24]. Preeclampsia is a major cause of perinatal complications, affecting 15–20% of pregnancies in women with T1D [14,28]. In our study, preeclampsia was strongly associated with preterm delivery (28% *vs* 3.3%, $P < 0.0001$; Table S3), which is in keeping with previous reports [10,29]. Of note, preeclampsia was also associated with indicated, but not spontaneous, preterm delivery (Table S4; see supplementary materials associated with this article online), as already reported [10]. Antihypertensive treatment during pregnancy in women with preexisting nephropathy and hypertension is likely to reduce the frequency of preeclampsia and preterm delivery [29–31]. Treatment with low-dose aspirin has also been recommended for prevention of preeclampsia [6], although evidence of its efficacy in women with T1D is limited [32]. In our study, the frequency of preeclampsia was low (8%), and 60% of cases were in women without preexisting nephropathy (data not shown) and therefore could not be anticipated. Thus, benefit may be expected with intervention for this risk factor at the individual level, although its magnitude may be limited on a population basis.

Unlike previous studies, no significant relationship between prepregnancy BMI and perinatal outcomes was observed in our study, whereas one population-based study of women with T1D found that overweight/obesity was associated with a higher rate of adverse pregnancy outcomes [33]. This discrepancy could be explained by the larger number of women and considerably greater prevalence of overweight/obese women (57%) in that study than in ours (28%). Nevertheless, as the prevalence of obesity is increasing in women with T1D [34], overweight and obese women should be encouraged to lose weight before conceiving [24].

HbA_{1c} at delivery was a strong predictor of good perinatal outcomes and the two secondary outcomes, in accordance with the reported relationship between adverse perinatal outcomes and higher HbA_{1c} values at 26 and 34 weeks of gestation [35]. In that study, adverse outcomes were significantly associated with HbA_{1c} levels $\geq 6.5\%$ [35]. Moreover, in our cohort, the association between good perinatal outcomes and HbA_{1c} was continuous (Fig. 1), thereby suggesting that the lower the HbA_{1c}, the better the perinatal outcome, which is consistent with the American Diabetes Association (ADA) recommendation of an HbA_{1c} target $< 6.0\%$ during pregnancy [5]. Indeed, in our study, an $HbA_{1c} < 6.0\%$ at delivery, achieved by 41% of women, was identified by ROC analysis as the best threshold for predicting a good outcome. However, this threshold does not allow accurate identification of infants at low risk of perinatal complications: an adverse perinatal outcome was observed in 40% of women with $HbA_{1c} < 6.0\%$ at delivery and, conversely, a good perinatal outcome was noted in 32% of women with $HbA_{1c} \geq 6.0\%$ at delivery.

Several non-exclusive hypotheses may explain these observations. First and physiologically speaking, blood glucose concentrations and HbA_{1c} values decrease during pregnancy [36], suggesting that the current therapeutic targets may still be too high [37]. Second, HbA_{1c} does not accurately reflect blood glucose values in a given individual, and the same HbA_{1c} value can be associated with a wide range of mean glucose concentrations [38]. However, currently ongoing studies using continuous glucose monitoring during pregnancy should resolve this issue. Third, besides glucose, many other factors not assessed by routine care are involved in fetal growth and may be involved in the occurrence of adverse outcomes [39].

In our cohort, CSII treatment was not associated with a good perinatal outcome (Table 3), which is consistent with the results of a recent meta-analysis [40]. Furthermore, CSII treatment was not associated with the frequency of macrosomia (data not shown), which is in keeping with the closely similar HbA_{1c} values observed during each trimester in women treated with CSII and those using multiple insulin injections (data not shown). Nevertheless, an unexpected finding of our study was the independent association of CSII treatment and term delivery (aOR: 3.00, 95% CI: 1.47–6.12, $P = 0.003$; Table S3). This was due exclusively to the lower rate of indicated preterm delivery in women treated with CSII compared with multiple injections, and may suggest a bias towards a lower rate of induced delivery in women treated with CSII.

In conclusion, in the present study, rates of severe congenital malformations and perinatal mortality in women with T1D were similar to those of the background French population. However, increased rates of less-severe adverse perinatal outcomes persisted, mainly macrosomia and late preterm delivery. In addition, our study identified modifiable risk factors, mainly gestational weight gain and glycaemic control, both of which could be targeted to further improve perinatal prognoses in women with T1D.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary materials (Tables S1–S4) associated with this article can be found at http://www.scincedirect.com at https://doi.org/10.1016/j.diabet.2018.04.007.

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