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Morbidité materno-fœtale associée au diabète de type 2 diagnostiqué en début de grossesse

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AVERTISSEMENT

Liste des abréviations

BMI :	Body mass index
DIP:	Diabete in pregnancy
DT1:	Diabète de type 1
DT2:	Diabète de type 2
GDM :	Gestational diabetes mellitus
HbA1c :	Hémoglobine glyquée
IMC :	Indice de masse corporelle
LGA :	Large for gestational age
SMBG:	Self-monitoring of blood glucose
T1DM:	Type 1 diabetes mellitus
T2DM:	Type 2 diabetes mellitus

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I) Résumé

Contexte

À mesure que la proportion de patients atteints de DT2 inconnu augmente, une nouvelle catégorie de troubles du glucose a été définie dans les recommandations de l'Association internationale d'étude de la grossesse et du diabète (IADPSG). Les patientes sont considérées comme ayant un diabète pendant la grossesse (« Diabete In Pregnancy » ou « DIP ») si leur glycémie dépasse les seuils de définition du DT2 en dehors de la grossesse. Ainsi, le but de cette étude était d'évaluer le taux de complications materno-foetales dans une population atteinte de « DIP » par rapport à un groupe de femmes atteintes d'un DT2 préexistant connu (« pregestational T2DM ») dans une grande cohorte traitée.

Méthode

Les résultats de 342 grossesses suivies dans un service universitaire spécialisé de diabétologie et soins anténataux entre 1997 et 2017 ont été examinés. Toutes ont été traitées pour atteindre des cibles glycémiques standardisées. Les femmes ont été séparées en 2 groupes : en « pregestational T2DM» (n=241) ou en « DIP » (n=101). Le DIP a été défini par un test biologique au premier trimestre montrant une glycémie à jeun supérieure ou égale à 1,26 g/l et/ou une HbA1c supérieure ou égale à 6,5%. Un critère composite de complication a été défini par l'association de prééclampsie, HELPP syndrome, transfert maternel ou néonatal en réanimation, embolie pulmonaire, hémorragie sévère de la délivrance, macrosomie, et score APGAR à 5 minutes inférieur à 7.

Résultats

Les femmes « DIP » étaient significativement plus jeunes (33,1 ± 5,6 vs 34,7 ± 5,3, p=0,015) et avaient plus fréquemment des antécédents de diabète gestationnel (p=0,005) que les femmes « pregestational T2DM ». L'IMC n'était pas significativement différent entre les 2 groupes. Les femmes « DIP » présentaient un taux d'HbA1c aux 1er et 2ème trimestres, un gain de poids pendant la grossesse et un ratio d'insuline en début et en fin de grossesse significativement plus bas (p<0,001).

L’hypertension artérielle gestationnelle, les accouchements prématurés, la césarienne, le poids important pour le terme (LGA), l'admission en réanimation néonatale et le score APGAR inférieur à 7 à 5 minutes étaient comparables aux taux observés dans le groupe « pregestational T2DM ». Il y avait une tendance à un taux plus faible de prééclampsie dans le groupe « DIP » (4% vs 10,4% p = 0,052). Le taux de complication materno-foetale selon notre critère composite était significativement plus faible dans le groupe « DIP » que dans le groupe « pregestational T2DM » (33.7% vs 45.6%, p = 0,04).

Conclusion

Malgré un dépistage précoce et un traitement optimal, les femmes porteuses de « DIP » gardent des complications obstétricales et néonatales plus importantes que dans la population générale. Nos résultats démontrent un sur-risque de complications selon le moment de diagnostic du diabète.

II) Introduction

1) Diabète et grossesse

L'obésité et la sédentarité ne faisant qu'augmenter, le taux de diabète de type 2 dans le monde a ainsi explosé, d'environ 100 millions de personnes en 1980, il est passé à plus de 400 millions depuis 2014 et devrait atteindre les 700 millions d'ici 2025, et ceci particulièrement chez les femmes passant d'environ 5% en 1980 à presque 8% en 2014, et apparaissant à un âge de plus en plus précoce (1).

La présence d'une hyperglycémie pendant la grossesse est de plus en plus fréquente. Elle a concerné environ 21,4 millions de naissances vivantes dans le monde en 2013 (2). Il existe différents types de diabètes, et particulièrement durant une grossesse : d'une part les diabètes préexistants à la grossesse, tels que le diabète de type 1 (DT1) ou le diabète type 2 (DT2), et d'autre part celui qui survient uniquement durant la grossesse ou diabète gestationnel (GDM). Alors que la majorité des cas étaient dus à un diabète gestationnel en 2013, il existait tout de même 16% de diabète préexistant à la grossesse, qu'il soit connu ou non diagnostiqué auparavant (2).

Dernièrement, la proportion de grossesses affectées par le diabète préexistant ne fait qu'augmenter. Ceci s'explique principalement par une importante augmentation de la fréquence du DT2 chez des patientes de plus en plus souvent porteuses d'une obésité, et à un âge de plus en plus jeune, mais aussi au recul de l'âge maternel (3).

En France, les données périnatales de la dernière enquête nationale de 2016 rapportées par l'INSERM (Institut National de la Santé et de la Recherche Médicale) et la DREES (Direction de la Recherche, des Études, de l'Évaluation et des Statistiques) ont montré une augmentation du taux de diabète préexistant à la grossesse, et en particulier du DT2, qui concernait 0,2% des grossesses, ceci associé à une augmentation du surpoids et de l'obésité, estimés respectivement à 20% et 12% en 2016, contre respectivement 17% et 10% en 2010 (4).

2) Nouveaux enjeux de la prise en charge du DT2 durant une grossesse

Parallèlement à cette prévalence qui augmente, on observe un intérêt croissant à étudier le devenir materno-foetal de ces grossesses compliquées par un DT2. En effet, même si ces patientes souffrent d'un trouble glycémique plus léger, les femmes atteintes de DT2 ont des résultats périnataux comparables à ceux des femmes atteintes de DT1 (5), et parfois même des taux de complications plus importants, ce qu'a montré dernièrement Clausen et ses collaborateurs au Danemark avec des résultats périnataux moins bons chez les femmes atteintes de DT2 par rapport à celles porteuses d'un DT1 et à la population générale (6).

Il a bien été établi que les principaux risques maternels comprenaient l'hypertension gravidique, la prééclampsie et la rupture prématurée des membranes chez ces patientes (7). Les taux d'induction du travail et de césarienne sont aussi élevés chez les femmes présentant un diabète préexistant, et ils ne changent pas de manière significative avec le temps malgré des améliorations du contrôle glycémique et des soins obstétricaux reçus (8). Les taux de macrosomie restent particulièrement élevés chez ces patientes, en grande partie liés à la prévalence accrue de l'obésité. Ainsi, des études nationales aux Pays-Bas, en Suède et en Finlande ne suggèrent aucune amélioration des taux de complications obstétricales et néonatales au cours des dernières décennies, et encore une fois ceci s'expliquait par l'augmentation de l'âge maternel, des taux de surpoids et d'obésité chez les femmes en âge de procréer, mais aussi par l'augmentation de la durée d'ancienneté du diabète. Nous savons aussi que des complications du diabète peuvent apparaitre ou s'aggraver durant ces grossesses (9).

Un dépistage précoce du diabète chez les femmes enceintes se justifie donc par son impact négatif majeur sur le devenir materno-fœtal. Bien que les effets de la détection précoce et du diagnostic du diabète gestationnel ne soient pas encore clairs, les preuves en faveur d'une prise en charge agressive du diabète pendant la grossesse sont déjà bien documentées (10).

3) Diagnostic de diabète durant la grossesse ou DIP

Ainsi, la prévalence croissante du diabète à travers le monde, l'âge précoce du DT2 et l'augmentation de l'âge maternel signifient que davantage de femmes atteintes de diabète non diagnostiqué sont enceintes.

À mesure que la proportion de patientes atteintes de DT2 non identifié augmentait, une nouvelle catégorie de troubles du glucose a été introduite selon les recommandations de l'Association internationale d'étude du diabète et de la grossesse (International Association of the Diabetes and Pregnancy Study Groups IADPSG), validées par la World Health Statistics WHO en 2013. Il a été établi que le diabète diagnostiqué pendant la grossesse ou « Diabetes In Pregnancy » (« DIP ») concerneraient les patientes dont les valeurs de glycémies sont supérieures aux seuils définissant le diabète en dehors de la grossesse: glycémie plasmatique à jeun ≥7 mmol/L et/ou glycémie à 2 heures ≥ 11,1mmol/L et/ou HbA1c ≥ 6,5%.

Il n'y a aucune étude jusqu'à présent concernant la survenue de complications materno-fœtales chez ces patientes qui sont donc prises en charge sans programmation de leur grossesse, car non connues et non suivies en pré-conceptionnel, pour lesquelles nous posons le diagnostic de « Diabete In Pregnancy » (« DIP »).

4) Objectifs et design de l'étude

Le but de cette étude est d'évaluer le taux de complications materno-fœtales dans une population présentant un diabète diagnostiqué pendant la grossesse (« DIP ») selon les nouvelles recommandations de l'Association internationale d'étude du diabète et de la grossesse (International Association of the Diabetes and Pregnancy Study Groups IADPSG), comparée à un groupe de femmes atteintes d'un DT2 préexistant et connu (« pregestational T2DM »).

Pour cela, nous avons recensé l'ensemble des grossesses des patientes diabétiques de type 2 ayant été suivies dans la structure pluri-disciplinaire du Centre Hospitalier Régional Universitaire de Lille et dont l'accouchement a eu lieu entre le 1er janvier 1997 et le 31 décembre 2017 à l'Hôpital Jeanne de Flandre. Les patientes souffrant d'un diabète d'un autre type ainsi que les grossesses gémellaires et celles non menées à terme ont été exclues. Nous avons aussi exclus les patientes avec un antécédent de chirurgie bariatrique. Nous avons ainsi recueilli et analysé les données démographiques, diabétologiques, métaboliques, obstétricales et néonatales de 342 grossesses chez 274 patientes, dont 101 patientes porteuses d'un « DIP ».

L'ensemble des résultats de cette étude est rapporté dans la publication ci-jointe.

III) Article

1) Abstract

OBJECTIVE

As the proportion of patients with unknown T2DM has been increasing, a new category of glucose disorder was introduced with the International Association of Diabetes Pregnancy Study Group (IADPSG) recommendations. Women are considered to have Diabetes In Pregnancy (DIP) if their plasma glucose values are above the thresholds defining diabetes outside of pregnancy. So, the aim of this study was to evaluate the rate of materno-fetal complication in a population with DIP compared to a group of women with pregestational T2DM in a large treated cohort.

RESEARCH DESIGN AND METHODS

Outcomes from 342 pregnancies attending in a university hospital antenatal diabetes clinic between 1997 and 2017 were examined. All were treated to standardized glycemic targets. Women were stratified as pregestational T2DM (n=241) or DIP (n=101). DIP was defined by a first-trimester biological test showing fasting blood glucose greater than or equal to 1.26 g/l and/or HbA1c greater than or equal to 6.5%. A composite criterion of complication was defined by the association of preeclampsia, hellp syndrome, maternal or newborn transfer to intensive care unit, pulmonary embolism, severe hemorrhage of delivery, macrosomia, and APGAR score at 5 minutes less than 7.

RESULTS

Women with DIP were significantly younger (33.1 ±5.6 vs 34.7 ±5.3, p=0.015) and had more frequently a history of gestational diabetes (p=0.005) than women with pregestational T2DM. The BMI was not significantly different between the 2 groups. The women with DIP had significantly lower HbA1c at 1st and 2nd trimester, gestational weight gain and insulin ratio in early and late pregnancy (p<0.001).

Hypertensive disorders, preterm delivery, caesarean section, large for gestational age, neonatal intensive care admission and APGAR score less than 7 at 5 minutes were comparable to rate seen in women with pregestational T2DM. There was a tendency of a lower rate of preeclampsia in the DIP group (4% vs 10.4% p=0.052). The rate of the composite criterion was significantly lower in the DIP group compared to the pregestational T2DM (33.7% vs 45.6%, p=0.04).

CONCLUSION

Despite early testing and best practice treatment, DIP women remains associated with poorer pregnancy outcome. Our results demonstrate a continuum of risk for adverse maternal outcome according to the timing of diabetes diagnosis.

2) Introduction

Hyperglycemia in pregnancy affected an estimated 21.4 million live births worldwide in 2013 (2). While the majority of cases were due to gestational diabetes (GDM), 16% were due to diabetes in pregnancy (known or previously undiagnosed) (2). The proportion of pregnancies affected by preexisting diabetes is increasing. This is primarily due to large increases in type 2 diabetes mellitus (T2DM) related to trends in obesity and later childbearing (3). In France, the perinatal data from the last national survey of 2016 reported by INSERM (Institut National de la Santé et de la Recherche Médicale) and DREES (Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques) showed an increase in the rate of pre-existing diabetes, particularly type 2, which concerned 0.2% of pregnancies, associated with an increase in overweight and obesity, estimated at 20% and 12% respectively (4).

Alongside the increasing prevalence, there has been an increasing interest in pregnancies complicated by T2DM in recent years. Despite the fact that they have a milder glycemic disturbance, women with T2DM have perinatal outcomes that are comparable to those of women with T1DM (5). In line with this, Clausen et al reported worse perinatal outcomes in women with T2DM than those in T1DM and in the background population (6). Maternal risks include pregnancy-induced hypertension, preeclampsia, and premature rupture of membranes (7). Rates of labor induction and caesarean section are high in women with preexisting diabetes, and have not changed significantly over time with improvements in glycemic control and obstetric care (8). Large for gestational age (LGA) and macrosomia rates remain high, largely explained by the increased prevalence of obesity (11). Nationwide studies from the Netherlands, Sweden and Finland suggest no improvement in either rates of serious adverse pregnancy outcomes or perinatal complications in recent decades, with possible explanations including increasing maternal age, longer duration of diabetes and increasing rates of overweight and obesity among women with reproductive years.

The rationale for early screening of women for overt diabetes in pregnancy lies in the significant adverse impact on pregnancy outcomes. While the effects of early recognition and diagnosis of GDM are not yet clear, the evidence supporting aggressive management of diabetes in pregnancy is well documented (10). The increasing prevalence of diabetes in most communities, the earlier age of onset of T2DM, and increasing maternal age mean that more women with undiagnosed diabetes usually T2DM are becoming pregnant. As the proportion of patients with unknow T2DM has been increasing, a new category of glucose disorder was introduced with the International Association of Diabetes Pregnancy Study Group (IADPSG) recommendations. Women are considered to have over diabetes or diabetes in Pregnancy (DIP) if their plasma glucose values are above the thresholds defining diabetes outside of pregnancy: fasting plasma glucose value ≥ 7 mmol/L and/or 2-hour glucose value ≥ 11.1 mmol/L and/or HbA1c ≥ 6.5%.

So, the aim of this study was to evaluate the rate of materno-fetal complication in a population with Diabetes in Pregnancy (DIP) compared to a group of women with pregestational T2DM.

3) Research design and methods

a) Study subjects

This observational retrospective study included a total of 342 women with T2DM who attended antenatal care and gave birth at the Department of Obstetrics, Jeanne de Flandres Hospital between 1997 and 2007. We included all patients with type 2 diabetes known before pregnancy, and those who received a first-trimester biological test showing fasting blood glucose greater than or equal to 1.26 g/l and/or HbA1c greater than or equal to 6.5% diagnosing an unknown type 2 diabetes and defined a new category of glucose disorder (Diabetes in pregnancy or DIP). We included singleton pregnancies beyond 24 weeks for which medical records for antenatal care and delivery were available.

The exclusion criteria were abortion, twin pregnancy, antecedent of bariatric surgery, and all other type of diabetes mellitus, including type 1 diabetes, monogenic diabetes and secondary diabetes. We defined two groups: pregestational type 2 diabetes as diabetes that has been diagnosed before pregnancy (“pregestational T2DM”), and Diabetes in pregnancy (“DIP”) according to the IADPSG recommendations.

b) Procedures

The T2DM pregnancies were managed according to our routine procedures for pregnancies. A diabetologic consult was done every month with a phone call twice a week by a specialized nurse to adjust diabetic treatment. Women performed SMBG (6times/day; fasting, before every meal, and after every meal). They were provided specific targets: < 1,00 g/l for fasting state, ≤ 1.20 g/l 2 hours after meals. HbA1c levels were measured every 4 weeks throughout pregnancy. HbA1c was measured monthly using automated high pressure liquid chromatography (normal range 4.0-6.0%). Insulin dose was titrated to the same blood glucose target. The standart regimen was basal bolus, with short-acting insulin analogues before meals and/or long-acting insulin analogues at bedtime. Women with T2DM treated with an insulin pump were continued. Additional obstetric and diabetes care was provided according to national guidelines.

c) Study outcomes measuress

Age, body mass index (BMI, defined as weight in kilograms divided by the square of height in meters), previous pregnancies, and smocking were collected in the files.

For patients with pregestational diabetes, we collected the date of type 2 diabetes diagnosis, type of treatment (multiple daily injections or insulin pumps or only dietary rules), history of arterial hypertension (defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or antihypertensive drug intake), of angina, of nephropathy (defined as albuminuria ≥ 30 mg/24h or renal insufficiency), of neuropathy, of retinopathy (defined by the result of the last fundus examination before pregnancy) and preconceptional HbA1c (defined as the last result of plasma HbA1c measured before pregnancy).

Concerning the complications of diabetes during pregnancy, retinopathy was assessed every 3 months by fundus examination or photography done by the same ophthalmologist. Concerning metabolic data, during pregnancy we collected the weight gain (in kilograms), insulin doses (in international units) and insulin ratio (in international units per kilograms and per day, using the early pregnancy weight).

Concerning obstetric complications, delivery term, start of work mode (spontaneous or triggering), and type of delivery (vaginal or caesarean) were collected.

Proteinuria and blood pressure was assessed every month. Proteinuria was defined as apparition of proteinuria ≥ 300 mg/24h or worsening of it during pregnancy. Pregnancy hypertension was defined as apparition of hypertension or worsening of it during pregnancy. Preeclampsia was defined as the association of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg and proteinuria ≥ 300 mg/24h after 20 weeks of amenorrhea. Vein thrombosis or pulmonary embolism, hellp syndrom (defined as association of hemolysis, elevated liver enzymes and low platelet count), hemorrhage of delivery (defined as volume greater than or equal to 500ml), and severe hemorrhage of delivery (defined as volume greater than or equal to 1000ml) was also collected.

Concerning newborns, birth weight (in kilograms), sex, cut, and cranial perimeter were assessed. We defined macrosomia as birth weight greater than 4000g, or than 90th percentile according to the formula AUDIPOG (which included the term, sex and birth weight). We defined prematurity as birth before 37 weeks of amenorrhea. The score APGAR at 1 and 5 minutes of life (from 0 to 10), transfer to the intensive care unit, heart rhythm disorders (defined by during dilation a flat rhythm, a bradycardia less than 100 beats per minute or a tachycardia greater than 180 beats per minute for more than 10 minutes, and during expulsion a bradycardia lasting more than 10 minutes), and breastfeeding mode (maternal, artificial, or mixed) were assessed.

We defined a composite criterion of complication defined by the association of preeclampsia, hellp syndrome, maternal transfer to intensive care unit, maternal pulmonary embolism, severe hemorrhage of delivery (volume greater than or equal to 1000ml), macrosomia (>=90th percentile), newborn transfer to the intensive care unit, and APGAR score at 5 minutes less than 7.

d) Statistical analyses

The quantitative variables were described using the mean and the standard deviation or the median and the interquartile range (IQR). The normality of the distributions was verified with the help of graphs and the Shapiro-Wilk test. The qualitative variables were described using frequencies and percentages. In case of sufficient sample size, the quantitative variables were compared between groups using Student T tests. In case of non-normality of data, non-parametric Wilcoxon tests were used. The comparison of the patients regarding the qualitative variables was performed using Chi-2 tests when the sample size was sufficient. In case of non-validity of these tests (expected counts < 5), Fisher's exact tests were used. The threshold of significance was 0.05. The analyses were performed using SAS software version 9.4 (SAS Institute, Cary NC, USA).

4) Results

In our study, we analyzed the data of 342 pregnancies: 101 pregnancies with Diabetes in Pregnancy (DIP) and 241 pregnancies with pregestational T2DM. Initially, we analyzed 456 patient files. We excluded 12 pregnancies with history of bariatric surgery, 14 twin pregnancies, 42 early miscarriages and 2 fetal deaths in utero after 24 weeks of pregnancy, and 44 pregnancies with another type of diabetes mellitus, including type 1 diabetes, monogenic diabetes and secondary diabetes.

a) Comparison of pre-pregnancy and diabetes characteristics in the 2 groups (table 1)

Women with pregestational T2DM were significantly older (34.7 ±5.3 vs 33.1 ±5.6 years old p=0.015) than women with DIP. But, we didn't find any significant difference of BMI in the 2 groups. The women with DIP have a higher rate of history of gestational diabetes than women with pregestational T2DM (p=0.005).

In the pregestational T2DM, the duration of diabetes was 3.8 ±4.5 years. In this group, 29.8% of the patients had an arterial hypertension under medication, 0.8% a history of angina, 4.9% a nephropathy, 2.1% a retinopathy, and 0.4% a neuropathy before pregnancy. During pregnancy, we didn't find any significant difference for retinopathy or proteinuria between the 2 groups. We had only 5 patients before pregnancy who had a retinopathy: 3 patients with a beginner stage 1, 1 patient with a moderate stage 3 and a duration of diabetes of 16 years, and 1 patient with a severe pan-photocoagulated stage whose duration of diabetes was 23 years. They did not worsen their retinopathy during pregnancy and had a good glycemic control. On the other hand, we had 14 retinopathy appearances, all of them with pregestational T2DM, and all of them in the second-trimester fundus. Their duration of diabetes was quite variable, from 2 to 13 years, and most had an HbA1c in early pregnancy not in the objectives, and then quickly normalized.

Table 1. Comparison of pre-pregnancy and diabetes characteristics in the 2 groups

Variables	Pregestational T2DM (n=241)	DIP (n=101)	P
Pre-pregnancy characteristics:			
-Mean age, years	34.7 ± 5.3	33.1 ± 5.63	**0.015**
-Mean weight, kg	95.4 ± 21.9	96.0 ± 20.20	0.80
-Mean BMI, kg/m2	35.4 ± 7.6	36.1 ± 7.01	0.44
-History of gestational diabetes, % (n)	35.3 (85)	51.5 (52)	**0.005**
-Multiparity, % (n)	83.0 (200)	84.2 (85)	0.21
-History of caesarean section, % (n)	36.1 (87)	26.7 (27)	0.13
Smocking, % (n)	11.2 (27)	5.9 (6)	0.13
Characteristics of diabetes:			
-Treatment during pregnancy:			
○ one/multiple daily insulin injections, % (n)	90.0 (217)	94.1 (95)	
○ insulin pumps, % (n)	9.1 (22)	1 (1)	
○ only diet, % (n)	0.8 (2)	5.0 (5)	
-Complications of diabetes before pregnancy:			
○ arterial hypertension, % (n)	29.8 (72)		
○ angina, % (n)	0.8 (2)		
○ nephropathy, % (n)	4.9 (12)		
○ retinopathy, % (n)	2.1 (5)		
○ neuropathy, % (n)	0.4 (1)		
-Complications of diabetes during pregnancy:			
○ proteinuria, % (n)	14.9 (36)	8.9 (9)	0.13
○ retinopathy, % (n)	5.8 (14)	0 (0)	

b) Comparison of glycemic control in the 2 groups (table 2)

As expected, maternal HbA1c levels decreased during pregnancy in the 2 groups. The mean of preconceptional HbA1c in the pregestational T2DM was 7.2% ±1.6. The women with DIP had a significantly lower HbA1c at 1st and 2nd trimester with a tendency at 3th trimester than the women with pregestational T2DM. The gestational weight gain was also significantly lower in the DIP group than in the pregestational T2DM ($p<0.001$). The insulin ratio was significantly lower in the DIP group than in the pregestational T2DM in early and late pregnancy ($p<0.001$).

Table 2. Glycemic control during pregnancy in the 2 groups

Variables	Pregestational T2DM (n=241)	DIP (n=101)	P
-Median HbA1c:			
○ 1st month, % (Q1;Q3)	6.8 (6.1 ; 7.7)	6.6 (6.1 ; 7.6)	0.60
○ 1st trimester, % (Q1;Q3)	6.5 (6.0 ; 7.3)	6.1 (5.6 ; 6.6)	**0.006**
○ 2nd trimester, % (Q1;Q3)	6.0 (5.6 ; 6.6)	5.7 (5.5 ; 6.2)	**0.009**
○ 3rd trimester, % (Q1;Q3)	6.0 (5.6 ; 6.5)	5.8 (5.4 ; 6.3)	0.060
-Median gain of weight, kg (Q1;Q3)	10.0 (6.0 ; 12.0)	6.0 (2.0 ; 10.0)	**<0.001**
-Median insulin ratio at the beginning of pregnancy, UI/kg/d (Q1;Q3)	0.4 (0.2 ; 0.8)	0.2 (0.1 ; 0.4)	**<0.001**
-Median insulin ratio at the end of pregnancy, UI/kg/d (Q1;Q3)	0.7 (0.4 ; 1.1)	0.5 (0.3 ; 0.8)	**<0.001**

c) Comparison of obstetric data in the 2 groups (table 3)

Mean gestational age at delivery was comparable in both groups. For maternal outcomes, we found no significantly difference in the two groups excepted a significantly lower rate of delivery hemorrhage in the DIP group (11.9% vs 23.7% p=0.013). There was a tendency of lower rate of preeclamsia in the DIP group than in the pregestational T2DM (4% vs 10,4% p=0.052). The onset of labour and the route of delivery were similar in both groups. There were no maternal death.

Table 3. Comparison of obstetric data in the 2 groups

Variables	Pregestational T2DM (n=241)	DIP (n=101)	P
Obstetrical characteristics:			
-Median term, weeks (Q1;Q3)	38±0.4	38.1±0.5	0.20
-Mode of onset of work:			
○ spontaneous, % (n)	18.4 (45)	27.7 (28)	0.16
○ induction, % (n)	61.1 (147)	54.5 (55)	
-Caesarean section, % (n)	51 (121)	41 (41)	
Obstetrical complication:			
-Pregnancy hypertension, % (n)	11.2 (27)	7.9 (8)	0.36
-Preeclampsia, % (n)	10.4 (25)	4.0 (4)	0.052
-Transfers in intensive care unit, % (n)	2.5 (6)	0.0 (0)	
-Delivery hemorrhage:			
○ >=500ml, % (n)	23.7 (57)	11.9 (12)	**0.013**
○ >=1000ml, % (n)	5.4 (13)	2.0 (2)	0.25
-Pulmonary embolism, % (n)	0.8 (2)	0.0 (0)	

d) Comparison of neonatal outcomes in the 2 groups (table 4)

The newborns of the patients with pregestational T2DM had higher birth weight and rate of macrosomia. The transfers in intensive care unit, and heart rhythm disorders (significantly) were also more important. Among the 23 newborns with malformations, 18 were from these 241 patients, and the majority was a cardiac malformation.

Neonatal outcomes in women with pregestational T2DM and DIP are presented in Table 4. Similary the incidence of macrosomia, LGA, transfert in intensive care unit and APGAR score were not significantly different in the 2 groups excepted a lower rate of heart rhythm disorder in the DIP group.

Overall the 241 pregnancies with pregestational T2DM presented significantly more complications according to our composite criterion of maternal and neonatal complication (45.6% vs 33.7% p=0.04).

Table 4. Comparison of neonatal outcomes in the 2 groups

Variables	**Pregestational T2DM (n=241)**	**DIP (n=101)**	**P**
Neonatal complications:			
-Prematurity, % (n)	18.7 (45)	13.9 (14)	0.28
-Median birth weight, g (Q1;Q3)	3370 (3020;3760)	3280 (2890;3690)	0.23
-Macrosomia (>=4000g), % (n)	18.3 (44)	15.8 (16)	0.59
-Macrosomia (>=90%), % (n)	29.5 (71)	21.8 (22)	0.15
-Transfers in intensive care unit, % (n)	10.0 (24)	7.9 (8)	0.55
-Heart rhythm disorders, % (n)	29.5 (71)	17.8 (18)	**0.025**
-APGAR at 1 minute less than 7, % (n)	7.4 (18)	3.9 (4)	0.25
-APGAR at 5 minutes less than 7, % (n)	1.2 (3)	2.9 (3)	0.65
-Complication (composite criterion°), % (n)	45.6 (110)	33.7 (34)	**0.04**

° composite criterion of complication: association of preeclampsia, hellp syndrome, maternal transfer to intensive care unit, maternal pulmonary embolism, severe hemorrhage of delivery (volume greater than or equal to 1000 ml), macrosomia (>=90th percentile), newborn transfer to the intensive care unit, and APGAR score at 5 minutes less than 7.

5) Conclusion

To our knowledge, the present population-based cohort study is the first to evaluate the materno-fetal complications associated with “Diabetes in Pregnancy” according to the IADPSG recommendations. In this large cohort study, we found that despite early testing and intensive intervention, “Diabetes in Pregnancy” in high-risk women was still associated with adverse pregnancy outcomes, including preterm delivery, caesarean section, macrosomia, LGA, and neonatal intensive care admission which are comparable to those of women with pregestational T2DM. Despite this intensive treatment regimen, our results demonstrate a continuum of risk for adverse maternal outcome according to the timing of diabetes diagnosis.

Regarding the characteristics of our global population, our patients are younger and more obese compared to the data of the literature (12, 13). Smoking is estimated at 9.6%, but less present than in other recent studies, where it can reach up to 21% (14, 15). Compared to the recent data from the 2016 national perinatal survey in France, our patients have much higher complication rates than the general population. For example, the general population has a lower rate of caesarean section (19.6%). Transfer rates in neonatal intensive care unit (2.4%), macrosomia (6.8%) and severe delivery hemorrhage (1.8%) are also lower. It should be noted that these patients are more often smokers (16.5%), but have much less history of hypertension before pregnancy (<1%). In this collection of national data, the proportion of patients with type 2 diabetes is estimated at 0.2% (4). Mackin et al. analysed episode-level data on all obstetric in patient delivery events, between 1998 and 2013, in 1452 mothers with T2DM from the national diabetes database (14). Compared with women without diabetes, delivery occurred 2 weeks earlier (37.3±2.4 weeks vs 38.0±0.4 weeks in pregestational T2DM group and 38.1±0.5 in DIP group). The proportion of preterm delivery was 21.8% compared to 18.6% in our T2DM group. The proportion of elective caesarean section and emergency caesarean section were respectively 30.5% and 29.1%, compared to 51% in our study. The proportion of LGA was 38.4% compared to 29.5% in our study (14). However, we didn’t have obstetrical and neonatal data in the literature for the “Diabetes in Pregnancy” group.

In our study, we demonstrated that the classical adverse outcomes are not significantly different between the T2DM and DIP groups excepted for the rate of delivery hemorrhage and the heart rhythm disorders which are significantly lower in the DIP group. The excessive risk for both neonatal and maternal complications, and an increased risk for a caesarean section among women with diabetes have been reported in many studies. The impact of diabetes on complications directly related to delivery is much less studied. Pallasmaa et al. studied the incidence of severe complications and he has showed that women with type 1 diabetes mellitus had a similar rate of any type of severe complications as did non-diabetic women (16).

Several studies show that obese women have a higher risk of obstetric hemorrhage than women with normal weight (17, 18). A Dutch study documented that obesity increased severe acute maternal morbidity in a dose dependent manner, but there was no association with major obstetric hemorrhage (19). Many studies do not separate the different modes of delivery, but Fyfe et al. did study postpartum hemorrhage in obese women related to caesarean section and vaginal delivery and reported that the risk for postpartum hemorrhage increased 1.7-fold in caesarean section and 2.1-fold in vaginal delivery (17). In our study, the BMI was similar in the 2 groups. We have showed that women with DIP had a lower rate of obstetric hemorrhage than women with T2DM. In many studies, this outcome is not reported. We can't exclude the impact of diabetes especially in T2DM according to the duration of diabetes. More recently, a nationwide study demonstrated that the risks of a low APGAR score and severe asphyxia-related neonatal morbidity were similarly increased in the offspring of mothers with T1DM and T2DM. In stratified analyses, they have found that overweight and obesity were associated with increased risk of a low APGAR score and severe asphyxia-related neonatal morbidity in the offspring of both mothers with T1DM and without diabetes. In the offspring of mothers with T2DM, the increased risk of a low APGAR score and severe asphyxia-related neonatal morbidity were partly attributed to their mothers' increased rates of overweight and obesity (20). In our study, we didn't find any difference of percent of low APGAR score between the 2 groups. But we have shown a lower rate of heart rhythm disorders during the labour in the DIP group compared to the T2DM group. The mechanism behind these findings is unclear. Our group has recently demonstrated that the fetuses of type 1 diabetic mothers showed evidence of altered heart rate variability, with a decreased autonomic ratio suggestive of a shift towards parasympathetic predominance (21).

When we used a composite criterion, women with DIP presented less complication than women with T2DM without reach the rates of the general population. We can speculate that this is probably already due to the fact that these women with DIP were younger, with a better glycemic balance from the beginning to the end of pregnancy. As expected, HbA1c decreased in each group during pregnancy. A recent study has already investigated the occurrence of placental pathology and neonatal complications according to the HbA1c level in early pregnancy of patients with T2DM. They have showed that HbA1c levels in early pregnancy are weak predictors (22). But this study didn't currently focus on the duration of diabetes in these patients, but more often on the occurrence of obstetric complications depending on the date of early management during pregnancy especially in preconception (23).

In our study, we focused on the insulin requirements during pregnancy. It is very interesting to note than women with T2DM had higher insulin requirements at the beginning and at the end of pregnancy than those with DIP. Compared to Padmanabhan et al. 's study, the insulin requirement in women with T2DM are similar at the first trimester but lower at the end of pregnancy (24). Outside of pregnancy, it is known that women with T2DM have greater insulin resistance than T1DM, so it is possible that the magnitude of physiological insulin resistance in pregnancy is also greater in women with T2DM. We can speculate than women with T2DM and women with DIP produce different amounts of placental hormones leading to these differences in insulin requirements. BMI and weight gain may also contribute to the differences in insulin requirements observed in the literature. Conversely to Padmanabhan's results, only the weight gain was significantly difference between the two groups in our study.

We didn't know if the duration of diabetes could have an influence but it is interesting to precise that these women with DIP had no complication of diabetes as retinopathy. All these patients had a fasting blood glucose level above 1.26g/l in early pregnancy, but for all that, HbA1c levels were not necessarily higher than 6.5%. HbA1c was below than 6.5% in 56% of women with DIP in favor of a normal glucose tolerance before pregnancy.

Some potential limitations require discussion. This cohort study covers a period of 20 years, thereby comprising a large population of women with T2DM but we collected the data retrospectively. The DIP cohort was a preselected high-risk group, and we lacked a control cohort to assess outcomes among women with DIP without early intervention.

In summary, this is the first data set comparing outcomes in women with DIP diagnosed in early pregnancy in comparison with those with T2DM. This study demonstrates that, despite intensive intervention, DIP in high-risk women is associated with suboptimal outcomes, and that this increased risk is associated with moderate dysglycemia. Moreover, outcomes for those women in whom DIP was diagnosed at the first trimester are approximate those of women with preexisting diabetes. Thus, women with DIP represent a high-risk cohort requiring systematic early identification and intensive surveillance. Given the persistence of poor outcomes in this cohort, despite early testing and current best practice treatment, prospective studies are needed to address residual risk factors and establish the efficacy of alternative glycemia and lifestyle management approaches in these high-risk pregnancies.

IV) Discussion

Notre étude a mis en évidence que les patientes définies comme ayant un « Diabete in pregnancy » ou « DIP » selon la nouvelle classification de l'IADPSG et de l'OMS étaient significativement plus jeunes, avaient plus souvent des antécédents de diabète gestationnel, un meilleur équilibre glycémique notamment aux 1er et 2ème trimestres, une prise de poids moindre durant la grossesse que les patientes ayant un DT2 prégestationel. Par ailleurs, les besoins insuliniques sont moins importants au cours de la grossesse que les patientes avec un DT2. Sur le plan de la morbidité materno-fœtale, il n'existe pas de diminution de complications en dehors du taux d'hémorragie de la délivrance. L'utilisation d'un critère composite évaluant les complications materno-foetales les plus graves nous a permis de démontrer que ces patientes avaient globalement moins de complications materno-foetales en terme de sévérité de complications. Pour autant, il a permis de montrer que les femmes porteuses d'un « DIP » avaient une morbidité materno-foetale plus élevée que celle de la population générale si on se fie aux résultats de l'enquête périnatale de 2016 en France (4), et ceci malgré un dépistage précoce du diabète et sa prise en charge intensive.

Cette étude nous laisse penser que ces patientes avec DIP sont une population ayant plus de risque que les patientes avec diabète gestationnel, se rapprochant des patientes avec DT2 mais dont la durée de diabète est beaucoup plus courte. Nous pouvons penser qu'en l'absence de prise en charge métabolique le taux de complications aurait été plus important.

L'originalité de ce travail fait que bien qu'il s'agisse de données rétrospectives, toutes ces patientes ont bénéficié d'une prise en charge métabolique et obstétricale par la même équipe médicale selon des protocoles identiques. A notre connaissance, il n'existe pas à ce jour d'études publiées s'intéressant à cette nouvelle entité de patientes avec un nombre aussi important en dehors du travail de Sweeting en 2016 qui a comparé 68 femmes dont le diabète a été diagnostiqué avant 12 semaines d'aménorrhée et dont la morbidité était finalement peu différente de celle des patientes DT2 (25).

Ainsi, des données prospectives sont nécessaires pour mieux étudier cette population et ses facteurs de risque résiduels, et déterminer des paramètres de contrôle glycémique optimaux en dehors de l'HbA1c. En effet, les besoins en insuline de ces patientes sont bien inférieurs aux DT2, en début et en fin de grossesse, suggérant une physiopathologie de l'insulinorésistance différente, et éventuellement la nécessité de s'intéresser aux profils glycémiques en lien avec le métabolisme physiopathologique.

Même si notre étude a recueilli sur 20 ans les données rétrospectives de 342 grossesses, les effectifs restent modestes et nous avons besoin d'études portant sur un plus grand nombre de patientes, que nous pourrions par la suite séparer en fonction de leur taux d'HbA1c en début de grossesse. En effet, dans notre série, plus de 50% des patientes avec un « DIP » avaient une HbA1c<6.5% en début de grossesse. Ceci permettrait de mieux les caractériser et les prendre en charge car ces différentes sous-populations ont probablement un risque de sévérité et de complication différent.

En dehors de ces différents aspects, il convient également d'avoir des données médico-économiques dans cette population. Elles sont actuellement prises en charge sur le plan des complications comme les patientes avec un DT2 prégestationnel. Il n'est pas démontré qu'en ce qui concerne le suivi des complications du diabète, celui-ci doive se faire comme celui des patientes avec un DT2 prégestationnel. Le meilleur exemple étant le suivi de la rétinopathie qui est proposé chaque trimestre à cette population comme pour les patientes avec un DT2 connu en prégestationnel.

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Date de Soutenance : 10 octobre 2018

Titre de la Thèse : Morbidité materno-fœtale associée au diabète de type 2 diagnostiqué en début de grossesse

Thèse - Médecine - Lille 2018

Cadre de classement : Diabétologie

DES + spécialité : Endocrinologie, diabétologie, maladies métaboliques

Mots-clés : Diabète de type 2, grossesse, complication materno-fœtale

Résumé :

Contexte : À mesure que la proportion de patients atteints de DT2 inconnu augmente, une nouvelle catégorie de troubles du glucose a été définie dans les recommandations de l'Association internationale d'étude de la grossesse et du diabète (IADPSG). Les patientes sont considérées comme ayant un diabète pendant la grossesse (« Diabete In Pregnancy » ou « DIP ») si leur glycémie dépasse les seuils de définition du DT2 en dehors de la grossesse. Ainsi, le but de cette étude était d'évaluer le taux de complications materno-foetales dans une population atteinte de « DIP » par rapport à un groupe de femmes atteintes d'un DT2 préexistant connu (« pregestational T2DM ») dans une grande cohorte traitée.

Méthode : Les résultats de 342 grossesses suivies dans un service universitaire spécialisé de diabétologie et soins anténataux entre 1997 et 2017 ont été examinés. Toutes ont été traitées pour atteindre des cibles glycémiques standardisées. Les femmes ont été séparées en 2 groupes : en « pregestational T2DM» (n=241) ou en « DIP » (n=101). Le « DIP » a été défini par un test biologique au premier trimestre montrant une glycémie à jeun supérieure ou égale à 1,26 g/l et/ou une HbA1c supérieure ou égale à 6,5%. Un critère composite de complication a été défini par l'association de prééclampsie, HELPP syndrome, transfert maternel ou néonatal en réanimation, embolie pulmonaire, hémorragie sévère de la délivrance, macrosomie, et score APGAR à 5 minutes inférieur à 7.

Résultats : Les femmes « DIP » étaient significativement plus jeunes (33,1 ± 5,6 vs 34,7 ± 5,3, p=0,015) et avaient plus fréquemment des antécédents de diabète gestationnel (p=0,005) que les femmes « pregestational T2DM». L'IMC n'était pas significativement différent entre les 2 groupes. Les femmes « DIP » présentaient un taux d'HbA1c aux 1er et 2ème trimestres, un gain de poids pendant la grossesse et un ratio d'insuline en début et en fin de grossesse significativement plus bas (p<0,001). L'hypertension artérielle gestationnelle, les accouchements prématurés, la césarienne, le poids important pour le terme (LGA), l'admission en réanimation néonatale et le score APGAR inférieur à 7 à 5 minutes étaient comparables aux taux observés dans le groupe « pregestational T2DM ». Il y avait une tendance à un taux plus faible de prééclampsie dans le groupe « DIP » (4% vs 10,4% p=0,052). Le taux de complication materno-foetale selon notre critère composite était significativement plus faible dans le groupe « DIP » que dans le groupe « pregestational T2DM » (33.7% vs 45.6%, p=0,04).

Conclusion : Malgré un dépistage précoce et un traitement optimal, les femmes porteuses de « DIP » gardent des complications obstétricales et néonatales plus importantes que dans la population générale. Nos résultats démontrent un sur-risque de complications selon le moment de diagnostic du diabète.

Composition du Jury :

Président : Pr Damien Subtil

Assesseurs : Pr Laurent Storme

Dr Hugues Courteville

Directrice : Pr Anne Vambergue