UNIVERSITÉ DE LILLE

FACULTÉ DE MÉDECINE HENRI WAREMBOURG

Année : **2023**

THÈSE POUR LE DIPLÔME D'ÉTAT

DE DOCTEUR EN MÉDECINE

Impact du poids de naissance sur la survenue de complications néonatales au cours de la grossesse de patientes diabétiques de type 1

Présentée et soutenue publiquement le 16 octobre 2023 à 16 heures
au Pôle Formation

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ABRÉVIATIONS

BMI : Body Mass Index

BW : Birth Weight

CGM : Continuous Glucose Monitoring

CHU : Centre Hospitalier Universitaire

CI : Confidence Interval

CNIL : Commission Nationale de l'Informatique et des Libertés

CSII : Continuous Subcutaneous Insulin Infusion

DT1 : Diabète de Type 1

FIT : Functional Insulin Therapy

GA : Gestational Age

GD : Gestational Diabetes

HbA1c : Hémoglobine glyquée

HTA : Hypertension Artérielle

ICU : Intensive Care Unit

IOM : Institute Of Medicine

IMC : Indice de Masse Corporelle

IUFD : Intra-uterine Fetal Death

LADA : Latent Autoimmune Diabetes in Adults

LGA : Large for Gestational Age/Large pour l'âge gestationnel

MFIU : Mort fœtale in utero

MODY : Maturity-Onset Diabetes of the Young

OMS : Organisation Mondiale de la Santé

OR : Odds Ratio

PN : Poids de naissance

RR : Risque Relatif

SD : Standard Deviation

SFD : Société Francophone de Diabétologie

SGA : Small for Gestational Age

T1D/T2D : Type 1 Diabetes/Type 2 Diabetes

WHO : World Health Organization

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I. RÉSUMÉ

Contexte et objectifs : Les complications materno-fœtales au cours des grossesses diabétiques de type 1 (DT1) demeurent supérieures à celles des patientes non diabétiques. L'excès de croissance fœtale (EPF) est l'une des complications fréquemment décrites et peut induire d'autres complications comme l'hypoglycémie néonatale ou la détresse respiratoire. Le but de cette étude était de déterminer l'impact du poids de naissance sur la survenue de complications néonatales au sein de cette population et d'en identifier les facteurs maternels prédictifs.

Matériel et méthodes : Étude observationnelle, rétrospective, monocentrique menée au sein du CHU de Lille entre 1997 et 2022. Nous avons recueilli les données métaboliques maternelles, obstétricales ainsi que les données pédiatriques. Nous avons analysé les complications néonatales en fonction de catégories et de percentiles de poids de naissance. Un critère composite fœtal a été utilisé et était positif si au moins un des éléments suivants était présent : hypoglycémie néonatale, détresse respiratoire, transfert néonatal et mort fœtale in utéro. Les résultats sont exprimés en Odds Ratio (OR) avec leurs intervalles de confiance (IC) à 95%.

Résultats : 797 grossesses de patientes DT1 ont été analysées. Les mères avaient en moyenne un âge de 29.5 (± 4.9) ans, un IMC de 25 (± 4.9) kg/m² et 36,6% étaient nullipares. La durée moyenne de diabète était de 14.8 (± 7.9) années. L'HbA1c pré-gestationnelle moyenne était de 7,5 (± 1,5) % et la plupart des patientes (70,7%) présentaient un diabète non compliqué. Le terme moyen à la naissance était de 37,4 (± 2) semaines. Le poids de naissance moyen était de 3520 (± 664) grammes, avec

22% de macrosomes et 52,8% de LGA. 8,4 % des nouveau-nés ont présenté une détresse respiratoire, 30,9 % une hypoglycémie et 12,4 % ont dû être transférés. Le critère composite fœtal était présent chez plus d'un tiers des nouveau-nés (38,5%). Nous avons montré un risque significativement accru d'hypoglycémie (OR = 1,670 (IC 95 % = 1,178 à 2,368)), de détresse respiratoire (OR = 3.087 (CI 95% = 1.606 à 5.932)) et de transferts néonataux (OR = 3.326 (IC 95% = 1.194 à 5.604)) dans la classe C4* (≥ 97ème percentile). En revanche, nous n'avons pas montré d'augmentation significative du risque de complications néonatales en fonction de la durée de diabète, la présence d'une rétinopathie ou du développement d'une prééclampsie. Seule la césarienne était associée à ce risque.

Conclusion : L'EPF est associé aux hypoglycémies néonatales et à la détresse respiratoire néonatale. Ces résultats confirment l'importance de la surveillance de la croissance fœtale et de la prévention de l'excès de prise de poids fœtal. Cependant, les facteurs conduisant à cet EPF sont encore à identifier.

Mots clés : Diabète de type 1, Poids de naissance, Complications néonatales

ABSTRACT

Background and objectives: Maternal-fetal complications in type 1 diabetic (T1D) pregnancies remain higher than in non-diabetic patients. Excessive fetal growth (EFG) is one of the most frequently described complications and can lead to other complications such as neonatal hypoglycemia or respiratory distress. The aim of this study was to determine the impact of birth weight on the occurrence of neonatal complications in this population and to identify predictive maternal factors.

Material and methods: Observational, retrospective, monocentric study conducted at Lille University Hospital between 1997 and 2022. We collected maternal, obstetric and pediatric metabolic data. We analyzed neonatal complications according to categories and percentiles of birth weight. A fetal composite criterion was used and was positive if at least one of the following was present: neonatal hypoglycemia, respiratory distress, neonatal transfer and fetal death in utero. Results are expressed as Odds Ratio (OR) with 95% confidence intervals (CI).

Results: 797 pregnancies of T1D patients were analyzed. Mothers had a mean age of 29.5 (± 4.9) years, a BMI of 25 (± 4.9) kg/m² and 36.6% were nulliparous. The mean duration of diabetes was 14.8 (± 7.9) years. The mean pre-gestational HbA1c was 7.5 (± 1.5) %, and most patients (70.7%) had uncomplicated diabetes. Mean term at birth was 37.4 (± 2) weeks. Mean birth weight was 3520 (± 664) grams, with 22% macrosomia and 52.8% LGA. 8.4% of neonates presented with respiratory distress, 30.9% with hypoglycemia and 12.4% required transfer. The fetal composite criterion was present in over a third of newborns (38.5%). We showed a significantly increased

risk of hypoglycemia (OR = 1.670 (CI 95% = 1.178 to 2.368)), respiratory distress (OR = 3.087 (CI 95% = 1.606 to 5.932)) and neonatal transfers (OR = 3.326 (CI 95% = 1.194 to 5.604)) in class C4* (≥ 97th percentile). In contrast, we showed no significant increase in the risk of neonatal complications according to the duration of diabetes, the presence of retinopathy or the development of preeclampsia. Only caesarean section was associated with this risk.

Conclusion: EFG is associated with neonatal hypoglycemia and neonatal respiratory distress. These results confirm the importance of monitoring fetal growth and preventing excess fetal weight gain. However, the factors leading to this EPF have yet to be identified.

Key words: Type 1 diabetes, Birth weight, Neonatal complications

II. INTRODUCTION

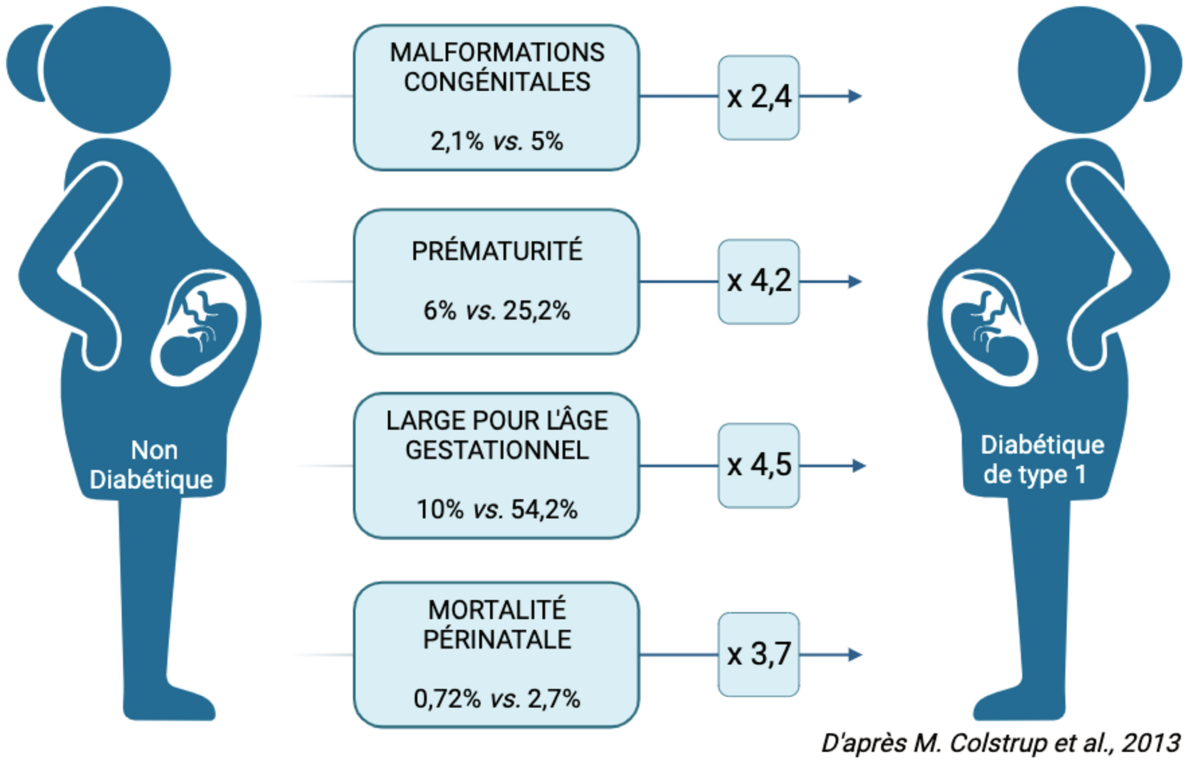
1) Diabète de type 1 et grossesse

En 2022, 537 millions de personnes vivaient avec un diabète dans le monde dont 8,75 millions avec un diabète de type 1 (DT1) (1). L'incidence du DT1 continue d'augmenter, de 3 à 4 % par an, et concerne des sujets d'âge jeune (2) notamment 50% de femmes, qui auront un jour un souhait de maternité.

Le diabète au cours de la grossesse est associé à un risque accru de complications materno-fœtales en comparaison à la population générale (3). Ce risque est d'autant plus marqué avec les diabètes préexistants à la grossesse, que ce soit le diabète de type 1 ou de type 2, en comparaison aux diabètes gestationnels (4).

En 1989, la Déclaration de Saint Vincent a fixé des objectifs afin d'améliorer la prise en charge des patients diabétiques en réduisant les complications liées au diabète et ainsi améliorer leur qualité de vie. Un des objectifs à 5 ans était notamment d'obtenir un risque de complications materno-fœtales au cours de la grossesse diabétique similaire à celui des femmes non diabétiques (5). Près de 35 ans plus tard, force est de constater que ces objectifs n'ont pas été atteints malgré une optimisation de la prise en charge diabétologique que ce soit via les nouvelles technologies (mesure continue du glucose, pompe ambulatoire à insuline, …) ou encore via des guidelines nationales et internationales strictes. Une revue semi-récente de la littérature réunissant 14 099 femmes DT1 (6), retrouve en comparaison à la population générale, un risque de malformations congénitales 2,4 fois plus élevé (5% *vs.* 2,1%), un risque de mortalité péri-natale 3,7 fois plus élevé (2,7% *vs.* 0,72%), un risque de prématurité 4,2 fois plus

élevé (25,2% *vs.* 6%) et enfin un risque d'excès de croissance fœtale 4,5 fois plus élevé (54,2% *vs.* 10%).



D'après M. Colstrup et al., 2013

Dans une étude britannique réalisée en 2021, réunissant 8690 patientes diabétiques de type 1, il persiste un risque élevé de LGA (52,2%), de prématurité (42,5%) et de transfert néonatal (43%) (7).

Les autres risques fœtaux fréquemment associés sont l'hypoglycémie néonatale, la dystocie des épaules, souvent liée à la macrosomie, la détresse respiratoire et le transfert en unité de soins continus ou en réanimation néonatale (8). Sur le plan maternel, il existe un risque accru de complications métaboliques (hypoglycémie, décompensation céto-acidosique), de risques obstétricaux (déchirures périnéales, hémorragie de la délivrance) et d'apparition ou aggravation de complications

microangiopathiques comme la rétinopathie (9) ou la néphropathie diabétique pouvant conduire à une prééclampsie (10).

2) Excès de croissance fœtale

L'excès de croissance fœtale est une complication fréquemment décrite chez les enfants nés de mères diabétiques. Il peut lui-même être responsable de complications maternelles comme des déchirures périnéales ou une hémorragie de la délivrance immédiate (définie par un saignement > 500 ml dans les 24 heures après l'accouchement) mais aussi de complications fœtales comme la dystocie cervicale, des fractures claviculaires ou des lésions du plexus brachial (11).

Un des mécanismes physiopathologiques souvent avancé dans l'excès de croissance est l'hyperinsulinisme fœtal secondaire à l'hyperglycémie maternelle. Les propriétés anabolisantes de l'insuline vont ainsi participer à l'augmentation du périmètre abdominal et à la prise de poids fœtale (12). De plus, la surexpression placentaire de transporteurs de glucose, comme GLUT-1, augmenterait le passage transplacentaire du glucose, même en l'absence d'hyperglycémie maternelle, et pourrait ainsi également contribuer à la prise de poids fœtale (13,14)

L'excès de croissance fœtale peut aboutir à une macrosomie fœtale, définie par un poids de naissance supérieur à 4000 g ou à un nouveau-né large pour l'âge gestationnel (LGA) défini par poids de naissance supérieur au 90ème percentile selon des courbes de référence. Bien que le contrôle glycémique au cours de la grossesse semble jouer un rôle important sur la croissance fœtale, la prévalence élevée de nouveau-nés LGA, malgré un contrôle glycémique satisfaisant, suggère l'implications

d'autres facteurs. Effectivement, un travail précédent issu de notre centre, sur 678 grossesses entre 1997 et 2019, avait montré que, malgré une correction du déséquilibre glycémique très tôt pendant la grossesse, persistait un risque de LGA chez les nouveau-nés de mères DT1, suggérant ainsi d'autres mécanismes d'implication (15).

De plus, un écueil possible est celui de l'appréciation de cette macrosomie. À l'heure actuelle, il n'existe aucun consensus national ou international sur les courbes de croissance fœtales les plus appropriées au cours de la grossesse chez les femmes DT1. On distingue les courbes de croissance standardisées, décrivant une croissance idéale à partir d'une population à faible risque, des courbes de croissance ajustées (ou individualisées) qui sont adaptées à une population ou un pays en prenant notamment en compte des caractéristiques maternelles. Les courbes de croissance selon AUDIPOG sont des courbes individualisées construites à partir d'une population française. Elles prennent en compte l'âge gestationnel, le sexe, le rang de naissance de l'enfant mais aussi l'âge, le poids pré-conceptionnel et la taille de la mère (16). Notre analyse se fondant sur le poids de naissance, notre choix s'est porté sur la courbe AUDIPOG.

3) Complications néonatales les plus fréquentes des enfants nés de mères DT1

- **Hypoglycémie néonatale**

L'hypoglycémie néonatale est une complication fréquemment décrite chez les enfants nés de mères diabétiques. Si ses effets à court terme sont plutôt bien connus, ses effets à moyen et long terme restent peu décrits. Lorsqu'elle est persistante, l'hypoglycémie néonatale peut entrainer des convulsions voire des lésions cérébrales.

Elle semblerait associée à un risque accru de troubles visuels, de troubles dysexécutifs ou de troubles de l'apprentissage comme la dyscalculie ou la dyslexie, bien que les données restent rares (17). L'identification de facteurs prédictifs reste donc essentielle à la prévention de ces hypoglycémies néonatales et de leurs possibles conséquences.

L'amélioration de l'équilibre glycémique au cours de la grossesse, notamment grâce aux nouvelles technologies comme la pompe à insuline et les systèmes en boucle fermée (18,19), semble jouer un rôle dans la prévention des hypoglycémies néonatales en limitant l'hypertrophie pancréatique et l'hyperinsulinisme fœtal réactionnel à l'hyperglycémie maternelle (12). A l'inverse, l'hyperglycémie maternelle au cours de la grossesse et lors de l'accouchement semble associé à un risque plus important d'hypoglycémie néonatale (20).

Une des difficultés qui persiste à ce jour est l'absence de consensus concernant la définition de l'hypoglycémie néonatale (17) :

Definition of neonatal hypoglycemia (mg/dl)

Institution, year	Time from birth					
	0–2 h	2–4 h	4–24 h	24–48 h	48–72 h	>72 h
AAP, 2011 (12)	<40 mg/dl		<45 mg/dl		<60 mg/dl	
ABM, 2014 (13)	<28 mg/dl		<40 mg/dl		<48 mg/dl	
PES, 2015 (14)		<50 mg/dl			<60 mg/dl	
BAPM, 2017 (15)		<45 mg/dl if symptomatic <36 mg/dl in asymptomatic at risk infants				
CPS 2019 (16)			<47 mg/dl			
SNG, 2019 (17)			<47 mg/dl			<54 mg/dl

AAP, American Academy of Pediatrics; BAPM, British Association of Perinatal Medicine; ABM, Academy of Breastfeeding Medicine; CPS, Canadian Pediatric Society; SNG, Swedish national guidelines; PES, Pediatric Endocrine Society.

De Angelis et al., 2021

En 2020, la Société Française de Néonatalogie, sur laquelle nous nous sommes appuyés pour notre travail, propose plusieurs niveaux d'intervention (21) :

- Au cours des 48 premières heures de vie :
    - Une glycémie < 0,45 g/l (2.5 mmol/l) associée à des signes cliniques
    - Une glycémie < 0,35 g/l (2 mmol/l) sans signes cliniques
- A partir du 3ème jour de vie :
    - Une glycémie < 0,50 g/l (2,7 mmol/l)

▪ Détresse respiratoire néonatale

La détresse respiratoire néonatale est une complication potentiellement grave et responsable d'une forte morbi-mortalité chez les nouveau-nés, notamment en cas de prématurité. Elle peut, entre autres, être secondaire à un retard de résorption du liquide amniotique, à une maladie des membranes hyalines, à une inhalation méconiale ou une infection materno-fœtale ou encore à une pathologie congénitale malformative (22). Le développement de la corticothérapie anténatale, permettant la synthèse du surfactant et la maturation pulmonaire, entre autres, a permis de réduire ce risque (23). Cependant, les enfants nés de mères DT1 restent plus à risque de détresse respiratoire néonatale. Un des mécanismes physiopathologiques avancé est le retard de sécrétion de phosphatidylglycérol, un lipide essentiel du surfactant pulmonaire fœtal, en cas de diabète maternel, perturbant ainsi sa composition et son action (24). En cas de détresse respiratoire, un recours à une ventilation non invasive ou invasive peut être nécessaire et conduire à un transfert en soins critiques ou en réanimation.

▪ Transfert néonatal en soins critiques

Les enfants nés de mères diabétiques de type 1 sont plus à risque de transfert néonatal que ce soit en lien avec une prématurité, une détresse respiratoire nécessitant un support ventilatoire ou des hypoglycémies nécessitant des apports

intra-veineux (4,7). Il existe une très grande variabilité des protocoles de prise en charge néonatale selon les pays et au sein des maternités d'un même pays.

4) Bibliographie : Complications néonatales, poids de naissance et diabète de type 1

Complications néonatales	Population étudiée Pays Date	Design	Principales données
Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands Evers et al., 2004	323 DT1 Pays Bas 1999 – 2000	Observationnelle Multicentrique (118)	Macrosomie = 52,5% Prématurité = 32,2% Hypoglycémie = 64% (< *0,47 g/l*) Détresse respiratoire = 15% MFIU = 1,8%
Determinants of a good perinatal outcome in 588 pregnancies in women with type 1 diabetes Lepercq et al., 2019	588 grossesses chez 441 DT1 France 2000 – 2014	Observationnelle Monocentrique	LGA = 41% (courbes de croissance françaises) Prématurité = 16% Hypoglycémie = 11% (< 0,40 dans les 3 premières heures de vie) Détresse respiratoire = 2,4% Transfert = 19%
Obstetric and perinatal outcomes in pregnancies complicated by diabetes, and control pregnancies, in Kronoberg, Sweden Stogianni et al., 2019	37 DT1 - 11 DT2 97 diabètes gestationnels Suède 2009 – 2012	Observationnelle Rétrospective Monocentrique	LGA = 60% (courbes de croissance non précisées) Poids de naissance > 4500g = 2,7% Prématurité = 35% Hypoglycémie = 32% (< 0,47 g/l dans les 24 premières heures de vie)
Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study Murphy et al., 2021	8690 DT1 - 8685 DT2 Royaume-Uni 2014 – 2018	Observationnelle Multicentrique (172)	LGA = 52,2% - SGA = 5,4% (courbes de croissance GROW) Prématurité = 42,5% - Grande prématurité = 9,2% Transfert = 43% MFIU = 1%
Risk factors for pregnancy outcomes in Type 1 and Type 2 diabetes Seah et al., 2021	92 DT1 - 106 DT2 - 119 contrôles Australie 2004 – 2014	Observationnelle Rétrospective Monocentrique	LGA = 63,4% - SGA = 5,4% (courbes de croissance personnalisées) Prématurité = 33,3% - Grande prématurité = 10,8% Hypoglycémie = 26,9% (< 0,47 g/l) Transfert = 19,4% MFIU = 2,2%
Retrospective national cohort study of pregnancy outcomes for women with type 1 and type 2 diabetes mellitus in Republic of Ireland Newman et al., 2022	696 DT1 – 374 DT2 Irlande 2015 – 2020	Observationnelle Rétrospective Multicentrique (18)	LGA = 58,5% - SGA = 0,9% (courbes de croissance non précisées) Prématurité = 30,4% Poids de naissance > 4000 g = 27,6% Poids de naissance > 4500 g = 9,4% MFIU = 0,6%

Poids de naissance	Population étudiée Pays Date	Design	Principales données
Large-for-gestational-age (LGA) neonate predicts 2.5-fold increased odds of neonatal hypoglycaemia in women with type 1 diabetes Yamamoto and al., 2017	161 grossesses DT1 Canada 2006 – 2010	Observationnelle Rétrospective Multicentrique (3)	LGA = 41,6% - SGA = 2,5% (courbes de croissance canadiennes) Prématurité = 32,3% - Grande prématurité = 6,2% Hypoglycémie = 36,6% (définition clinique selon note du pédiatre) et 37,9% (définition biologique < 0,47 g/l) Transfert = 47% Risque d'hypoglycémie néonatale multiplié par 3,8 en cas de LGA (définition clinique) Risque d'hypoglycémie néonatale multiplié par 2,5 en cas de LGA (définition biologique)
Large-for-Gestational-Age Neonates in Type 1 Diabetes and Pregnancy: Contribution of Factors Beyond Hyperglycemia McGrawth and al., 2018		Revue de la littérature	LGA est plus corrélé à la variabilité glycémique que le temps passé en hyperglycémie LGA plus corrélé à la prise de poids au cours de la grossesse qu'à l'IMC pré-conceptionnel LGA associé à des taux de HDL-cholestérol plus bas et des taux de triglycérides plus haut chez la mère, indépendamment de l'IMC, de la prise de poids et de l'HbA1c
Which growth standards should be used to identify large- and small-for-gestational age infants of mothers with type 1 diabetes? A pre-specified analysis of the CONCEPTT trial Meek and al., 2021	221 grossesses DT1 Internationale	Observationnelle Rétrospective Multicentrique	Macrosomie = 26,2% Prématurité = 39,6% Hypoglycémie = 25,3% Détresse respiratoire = 8,4% Transfert = 36,9% Augmentation du risque d'hypoglycémie et de transfert en cas de PN > 97,7^{e} percentile (OMS) Pas de surrisque de détresse respiratoire en cas de PN > 97,7^{e} percentile (OMS)

5) Objectifs de l'étude

La grossesse chez les patientes présentant un diabète antérieur à la grossesse, et notamment un diabète de type 1, est associée à un risque plus important de complications materno-fœtales. Ce risque persiste malgré l'amélioration de l'équilibre glycémique permis notamment par les nouvelles technologies comme les pompes sous-cutanées à insuline et les systèmes en boucle fermée.

L'identification de facteurs prédictifs maternels de complications fœtales et néonatales, comme l'excès de croissance fœtale, l'hypoglycémie néonatale, la détresses respiratoire ou le transfert en soins intensifs, pourrait permettre d'identifier les enfants les plus à risque pour leur proposer une prise en charge individualisée afin de prévenir la survenue de ces complications.

Le but de cette étude est de **déterminer l'impact du poids de naissance sur la survenue de complications fœtales/néonatales au cours de la grossesse diabétique de type 1**. Secondairement, nous avons tenté **d'identifier des facteurs maternels prédictifs de ces complications.**

Pour cela, nous avons recueilli l'ensemble des données des patientes diabétiques de type 1, suivies au sein de la structure Diabète et Grossesse et ayant accouchées au CHU de Lille entre 1997 et 2022 ainsi que les données de leurs enfants. Nous avons exclu les patientes qui présentaient une autre étiologie de diabète (diabète de type 2, diabète monogénique, diabète de type 1 lent, diabète LADA, diabète gestationnel, diabète secondaire), celles pour lesquelles un doute diagnostique persistait, les découvertes de DT1 au cours de la grossesse, les patientes mineures, les grossesses

multiples et les patientes perdues de vue ou ayant accouchées en dehors du CHU de Lille.

Ainsi, nous avons recueilli et analysé les données de 863 grossesses de patientes DT1. L'ensemble des résultats de ce travail vous est présenté sous forme d'un article scientifique, rédigé en Anglais, dans l'objectif d'une soumission dans un journal scientifique de rang satisfaisant :

III. ARTICLE

Impact of excess birth weight on neonatal complications during pregnancy in type 1 diabetic patients

ABREVIATIONS

BMI : Body Mass Index

BW : Birth Weight

CGM : Continuous Glucose Monitoring

CI : Confidence Interval

CSII : Continuous Subcutaneous Insulin Infusion

FIT : Functional Insulin Therapy

GA : Gestational Age

GD : Gestational Diabetes

HbA1c : Hemoglobin Glycated

ICU : Intensive Care Unit

IOM : Institute Of Medicine

IUFD : IntraUterine Fetal Death

LADA : Latent Autoimmune Diabetes in Adults

LGA : Large for Gestational Age

MODY : Maturity-Onset Diabetes of the Young

OR : Odds Ratio

RR : Relative Risk

SD : Standard Deviation

SGA : Small for Gestational Age

T1D/T2D : Type 1 Diabetes/Type 2 Diabetes

WHO : World Health Organization

INTRODUCTION

The prevalence of diabetes during pregnancy continues to grow around the world. Pregestational diabetes, and more particularly type 1 diabetes (T1D) during pregnancy, is associated with adverse pregnancy outcomes, both for the mother and the unborn child (25). The most frequently described fetal complications are prematurity, shoulder dystocia, neonatal hypoglycemia, increased rates of congenital anomaly and neonatal respiratory distress, which may lead to transfer to intensive care or neonatal care (8). Nevertheless, improvements in maternal metabolic parameters before and during pregnancy, notably through preconceptional management, have reduced some of these risks. However, their prevalence remains high, and far from the objectives set by the 1989 Saint-Vincent Declaration, namely to achieve pregnancy outcomes similar to those of non-diabetic women. In addition, the prevalence of certain complications such as excess fetal growth has increased over time. (6). Helen Murphy et al., in a recent English population-based observational study, reported a persisting high prevalence of neonatal morbidity with prematurity (42.5%), LGA (52.5%) and neonatal transfer (43%) (7).

Growth can be expressed by birth weight (> 4,000 grams or not) or by growth percentile. The growth percentile tells us where the child is in the distribution of percentiles (from < 3^{rd} to > 99^{th}). Excessive fetal growth can be responsible for maternal complications (perineal tear, obstetric hemorrhage, etc.) and fetal complications (cervical dystocia, clavicle fracture, brachial plexus injury, etc.) (11). Although glycemic control during pregnancy appears to play an important role in fetal growth, the high prevalence of large-for-gestational-age (LGA) neonates despite satisfactory glycemic control suggests the involvement of other factors. Moreover, we

had already demonstrated in our center that despite optimal management of glycemic control (HbA1c < 6% in the 3rd trimester) in a cohort of 678 women between 1997 and 2019, persisted a significantly higher risk of LGA in the population of newborns born to T1D mothers, suggesting other mechanisms of involvement (15). Among these potential factors, we can cite maternal excess gestational weight gain (26), glycemic variability (27) or immune mechanisms (28). From a pathophysiological point of view, we now know the link between these maternal-fetal complications and maternal glycemic variations (29). However, the underlying mechanisms have yet to be fully elucidated. Maternal glycemic control, by limiting fetal hyperinsulinism and excess growth, appears to play a role in the prevention of neonatal complications such as neonatal hypoglycemia, LGA and prematurity (30).

The aim of our study was to determine the link between excessive birth weight on the occurrence of neonatal complications (for each complication or by using a composite criterion) during pregnancies of women with type 1 diabetes. Subsequently, we tried to identify possible maternal predictors of these complications (hypoglycemia, respiratory distress, and neonatal transfer).

MATERIALS AND METHODS

Research design

This retrospective single-center observational study was carried out at the University hospital of Lille, France. All data were collected from archived or computerized records. They included maternal characteristics, obstetrical follow-up, delivery, and newborns characteristics data. In accordance with French law, patients were informed of the possible use of their personal data for research purposes, unless they refused. The

database was declared to the French Data Protection Authority (CNIL) and all data were anonymously analyzed.

All pregnant women with type 1 diabetes, monitored by the Diabetes and Pregnancy Unit, and who gave birth at Lille University Hospital between 1997 and 2022 were included. Exclusion criteria were age less than 18 years, other types of diabetes (type 2 diabetes, monogenic diabetes, Latent Autoimmune Diabetes in Adults (LADA), gestational diabetes or secondary diabetes), doubtful cause of diabetes, type 1 diabetes diagnosis during pregnancy, multiple pregnancies, lost to follow-up or delivery outside the University hospital of Lille. We later excluded miscarriages (< 22 weeks of amenorrhea) and abortions.

Data collection

Maternal characteristics, demographics, obstetrical and diabetes data were collected from the maternal records. The information in the medical records were obtained from a combination of medical consultations and twice-weekly calls from specialist nurses up to the 6^{th} month of pregnancy, and from outpatient department consultations from the 6^{th} month of pregnancy. All patients performed self-monitoring of blood glucose with targets of < 0.95 g/l before meals and < 1.20 g/l 2 hours after the start of the meal, in accordance with the recommendations of the French Society of Diabetology (31). Delivery data and newborns characteristic were collected from the delivery and pediatric records.

Pre-gestational weight and height were used to calculate pre-gestational body mass index (BMI = weight/height^2 in kg/m^2). Smoking status was assessed. Obstetrical history (parity, gravidity, history of macrosomia, history of miscarriage) was collected.

Regarding diabetes, we collected the year of diagnosis and the duration of diabetes, divided into 4 classes: class 1 = duration < 5 years, class 2 = duration ≥ 5 and < 10 years, class 3 = duration ≥ 10 and < 20 years, class 4 = duration ≥ 20 years. We reported the type of treatment (multiple subcutaneous injections or continuous subcutaneous insulin infusion (CSII)), the use of functional insulin therapy (FIT), the pregestational HbA1c, defined as the last known HbA1c value before pregnancy, and the HbA1c at each trimester of pregnancy. We collected data on the complications of diabetes and their evolution during the pregnancy: history of retinopathy (defined by the results of the last fundus examination before pregnancy) reassessed by a new fundus every 3 months, history of nephropathy (defined by albuminuria greater than 30 mg/24h or renal failure) reassessed every month, history of arterial hypertension (defined by blood pressure greater than 140/90 mmHg or anti-hypertensive treatment). Pre-eclampsia was defined by the presence of arterial hypertension and proteinuria greater than 300 mg/24h after 20 of gestational age (GA).

Concerning obstetric characteristics and maternal adverse outcomes, we collected delivery term, with prematurity defined by a delivery before 37 GA, moderate prematurity defined by a delivery between 32 and 37 GA, very prematurity defined by a delivery between 28 and 32 GA and extreme prematurity defined by a delivery before 28 GA. We also collected the mode of delivery and the conditions of realization: vaginal (induced or spontaneous labor) or cesarean section (scheduled or emergency). We reported post-partum hemorrhage (defined as bleeding > 500 ml in the case of vaginal delivery or > 1000 ml in the case of caesarean section, within 24 hours of delivery), ketoacidosis decompensation and maternal intensive care transfer.

Regarding newborns characteristics and neonatal adverse outcomes, we collected sex, birth height, head circumference, birth weight (BW) and birth weight percentile. Macrosomia was defined as birth weight > 4,000 grams, LGA according to the Audipog formula as weight > 90th percentile and SGA according to the Audipog formula as weight < 10th percentile. We defined 4 birth weight categories (Class 1 = BW < 3,000 g, Class 2 = BW ≥ 3,000 and < 4,000 g, Class 3 = BW ≥ 4,000 and < 4,500 g, Class 4 ≥ 4,500 g) and 4 birth weight percentile categories (Class 1 = < 10th percentile, Class 2 = ≥ 10 - < 90th percentile, Class 3 = ≥ 90 - <97th percentile, Class 4 = ≥ 97th percentile). The use of antenatal corticosteroid therapy was reported. We collected Apgar scores at 1 and 5 minutes (with a score < 7 indicating poor adaptation to extra-uterine life) and umbilical arterial pH (with a pH < 7 defining severe neonatal acidosis). We reported acute respiratory distress, the need for intubation or transfer to a continuous care unit or intensive care unit and intrauterine fetal deaths (IUFD), defined as death after 22 weeks of amenorrhea (fetal viability threshold). Finally, we collected data on neonatal hypoglycemia, defined as a blood glucose level < 0.35 g/l in the first 48 hours of life or < 0.40 g/l after 48 hours of life, and on the use of a glucose infusion. We defined a fetal composite criterion composed of hypoglycemia, respiratory distress, neonatal transfer and IUFD. The criterion was positive if at least one of the elements was present.

Statistical analyses

Categorical variables are expressed as frequency and percentage and quantitative variables as means ± standard deviation in case of normal distribution or medians (interquartile range, IQR) otherwise. Normality of distributions was checked graphically and using the Shapiro-Wilk test. Association of weight measures (birth weight, macrosomia, LGA, SGA) with each fetal outcome (hypoglycemia, respiratory distress,

transfer and the composite criteria) was evaluated using a logistic regression model (adjusted on term for birth weight and macrosomia) (or using Fisher's exact test in case of complete separation). For quantitative variables, we assessed the log-linearity assumption by using restricted cubic spline functions, in case of non-log-linear association we categorized the variable. Odds ratios and their 95% confidence interval were derived from models as effect sizes. No statistical comparisons were done for categorical variables with frequency <5. Statistical testing was conducted at the two-tailed α-level of 0.05. Data were analyzed using the SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Demographic characteristics of type 1 diabetes population:

A total of 1,725 pregnancies in women with pregestational diabetes were identified, 862 of which had one of the exclusion criteria: 801 pregnancies with another cause of diabetes (type 2, MODY, LADA), 15 pregnancies with a doubtful cause of diabetes, 14 type 1 diabetes discovered during pregnancy, 12 multiple pregnancies, 5 underaged patients and 15 deliveries outside Lille University Hospital. We therefore identified 863 pregnancies in women with pregestational type 1 diabetes. We excluded 59 miscarriages and 7 abortions. Ultimately, 797 births were analyzed, including 791 alive birth and 6 intra uterine fetal deaths (*Figure 1*).

Baseline maternal characteristics :

These characteristics are shown in *Table 1*. The mothers were on average 29.5 (± 4.9) years old and had an average BMI of 25 (± 4.9) kg/m². 291 (36,6%) patients were nulliparous and 168 (27%) were smoking before pregnancy, 91 (15.2%) of them still

smoked during pregnancy. The average duration of diabetes was 14.8 (± 7.9) years. Regarding treatment, 475 (59.6%) patients were treated with continuous subcutaneous insulin infusion and 243 (30.5%) were using FIT before pregnancy. Average pregestational HbA1c was 7.5 (± 1.5) % and only 23.9% had a pregestational HbA1c < 6,5%, as recommended by the ADA. Most patients (70,7%) had uncomplicated diabetes prior to pregnancy. Regarding pregestational complications, 206 (25.8%) patient presented diabetic retinopathy, 52 (6,5%) presented diabetic nephropathy and 27 patients (3,4%) had hypertension.

Newborn characteristics:

These characteristics are shown in *Table 2.* 392 (49.3%) of the newborns were female and the mean gestational age at birth was 37.4 (± 2) weeks. 128 (16.3%) newborns had received antenatal corticosteroid therapy. 462 (76.6%) of births were induced and 406 (51.1%) were vaginal. Mean birth weight was 3520 (± 664.0) grams, and 22% of the newborns weighted over 4000 g and were therefore macrosomic. 52.8% were above the 90th percentile, meaning LGA. Mean height 49.3 (± 2.4) cm and mean head circumference 34.8 (± 1.9) cm.

Maternal end fetal adverse pregnancy outcomes:

Regarding the evolution of diabetic complications during pregnancy, 187 (23.6%) patients developed or worsened their retinopathy and 177 (22.3%) their proteinuria. 124 (15.6%) patients developed gestational hypertension and 87 (11.0%) pre-eclampsia. 264 (33.1%) patients required an emergency caesarean section and 84 (10.5%) suffered a post-partum hemorrhage. Finally, 23 (2.9%) patients suffered

ketoacidosis decompensation during their pregnancy and 9 (1.1%) were transferred to the ICU (*Table 3*).

In terms of fetal adverse events, 172 (21.6%) infants were born prematurely and the majority presented with moderate prematurity (84.9%). The macrosomia rate was 22% (174), the LGA rate 52.8% (401) and the SGA rate 1.8% (14), according to the AUDIPOG formula. Regarding adaptation to extra-uterine life, 76 (9.6%) newborns had an Apgar score of lower than 7 at one minute and 15 (1.9%) still lower than 7 at 5 minutes. An arterial pH below 7 was found in 17 (2.2%) newborns. 65 (8.4%) newborns presented with respiratory distress in the first few hours of life, 18 (28.1%) being intubated. 239 (30.9%) newborns presented hypoglycemia and 102 (42.7%) of them required intravenous glucose perfusion. We recorded 98 (12.4%) neonatal transfers, including 36 (36.7%) to a resuscitation ward and 6 (0.8%) intrauterine fetal deaths. Finally, the fetal composite criterion was found in more than a third of newborns born to T1D mothers (38.5%).

Birth weight and fetal outcomes

The newborns were divided into different classes according to their birth weight: 134 (16.9%) were in class 1 (C1) defined by weight under 3000 grams, 483 (61.1%) in class 2 (C2) defined by weight between 3000 and 4000 grams, 138 (17.4%) in class 3 (C3) defined by weight between 4000 and 4500 grams and 36 (4.6%) in class 4 (C4) defined by weight over 4500 grams.

They were also classified according to the percentile associated with their birth weight and birth term: 13 (1.7%) were in class 1 (C1*) defined by weight below the 10^{th}

percentile, 345 (45.5%) were in class 2 (C2*) defined by weight between the 10th and 90th percentiles, 136 (17.9%) were in class 3 (C3*) defined by weight between the 90th and 97th percentiles and 265 (34.9%) were in class 4 (C4*) defined by weight above the 97th percentile.

- *Comparison of fetal adverse outcomes according to birth weight classes and percentiles:*

Table 4 presents the impact of extreme birth weight on fetal adverse outcomes. C2, defined as weighing between 3000 and 4000 grams, and C2*, defined by a weight between the 10th and 90th percentile, were chosen as references. C4 and C4* presented significantly more hypoglycemia with OR = 2.263 (CI 95 % = 1.120 to 4.574, p = 0.0229) and OR = 1.670 (CI 95 % = 1.178 to 2.368, p = 0.0338) respectively. Newborns with a higher birth weight percentiles presented significantly more respiratory distresses (C3* OR = 2.244 (CI 95% = 1.010 to 4.987, p = 0.0473) and C4* OR = 3.087 (CI 95% = 1.606 to 5.932, p = 0.0007)). Neonatal transfers were significantly higher in C3 (OR = 2.462 (CI 95% = 1.258 to 4.816, p = 0.0085)) and C4* (OR = 3.326 (CI 95% = 1.194 to 5.604), p = < 0,0001)). Finally, regarding the composite criterion, the risk was significantly higher in C4 (OR = 2.216 (CI 95% = 1.086 to 4.522, p = 0.0287)) and C4* (OR = 1.767 (CI 95% = 1.276 to 2.447, p = 0.0006)). We were unable to carry out analysis in C1* because the number of patients was too small, confirming the rarity of SGA in T1D.

- *Comparison of fetal adverse outcomes according to macrosomia and LGA:*

These results are presented in *Table 5*. Macrosomic infants had a higher risk of hypoglycemia (OR = 1.579 (CI 95% = 1.100 to 2.267, p = 0.0132)) and respiratory

distress (OR = 2.190 (CI 95% = 1.128 to 4.253, p = 0.0206), but not neonatal transfer (OR = 1.722 (CI 95% = 0.923 to 3.213, p = 0.0874)). LGAs had a higher risk of hypoglycemia (OR = 1.609 (CI 95% = 1.172 to 2.209, p = 0.0032)), respiratory distress (OR = 2.006 (CI 95% = 1.161 to 3.468, p = 0.0127)). Regarding the composite criterion, LGA children had a statistically significant risk of presenting one of its components (OR = 1.591 (CI 95% = 1.191 to 2.125, p = 0.0017)), unlike macrosomic children (OR = 1.387 (CI 95% = 0.979 to 1.964, p = 0.0656)).

Can certain maternal characteristics predict the onset of these neonatal complications?

After LGA, we then sought to identify other factors, especially maternal ones, that could influence the occurrence of the main neonatal complications. These results are shown in *Table 6.* The duration of diabetes was classified into four classes: class 1 (D1) defined by a duration strictly less than 5 years, class 2 (D2) defined by a duration between 5 and 10 years, class 3 (D3) defined by a duration between 10 and 20 years and class 4 (D4) defined by a duration greater than or equal to 20 years.

Regarding the risk of hypoglycemia, there was no significant difference between the four duration of diabetes classes. There was also no significant difference according to the presence of retinopathy (OR = 1.229 (CI 95% = 0.871 to 1.734, p = 0.2402)) or the onset of preeclampsia (OR = 1.174 (CI 95% = 0.720 to 1.913, p = 0.5203)). Infants born by emergency caesarian section presented a higher risk of hypoglycemia (OR = 2.154 (CI 95% = 1.562 to 2.971, p < 0.0001)).

For respiratory distress, the risk was lower in D2 (OR = 0.244 (CI 95% = 0.066 to 0.898, p < 0.0338). There was no significant difference according to the presence of

retinopathy (OR = 0.627 (CI 95% = 0.327 to 1.279, p = 0.2108)) or the onset of preeclampsia (OR = 1.120 (CI 95% = 0.523 to 2.399, p = 0.7701)). Infants born by emergency caesarian section presented a higher risk of respiratory distress (OR = 1.998 (CI 95% = 1.129 to 3.537, p = 0.0175)).

Regarding neonatal transfer, there was no significant difference between the four duration of diabetes classes. There was also no significant difference according to the presence of retinopathy (OR = 0.930 (CI 95% = 0.518 to 1.670, p = 0. 8092)) or the onset of preeclampsia (OR = 1.038 (CI 95% = 0.511 to 2.106, p = 0.9182)). Infants born by emergency caesarian section presented a higher risk of neonatal transfer (OR = 1.702 (CI 95% = 1.005 to 2.884, p = 0.0479)).

Finally, regarding the composite criterion, there was no significant difference between the four duration of diabetes classes, according to the presence of retinopathy or the onset of preeclampsia. Infants born by emergency caesarian section presented a higher risk of neonatal complications (OR = 1.915 (CI 95% = 1.389 to 2.640, p < 0.0001)).

DISCUSSION

The aim of our study was to determine whether there is an association between excessive birth weight and the occurrence of neonatal complications in newborns to type 1 diabetic mothers, with particular attention to hypoglycemia, respiratory distress and neonatal transfer to intensive care. We also sought to identify other possible predictors such as duration of progression of diabetes, worsening of retinopathy, preeclampsia or even cesarean section, of these complications. First, in this large

cohort of newborns of T1D mothers, our results show that the presence of excess birth weight of newborns is very common. Just over one in five newborns suffered from macrosomia and more than half were considered large for gestational age. Furthermore, our results interestingly confirm that this has consequences, since higher birth weight is significantly associated with an increased risk of neonatal hypoglycemia and respiratory distress. However, the other maternal parameters that we examined do not appear to be predictive of these neonatal complications other than cesarean section.

In preconception, our population has the same characteristics as other cohorts in the literature in terms of age, duration of diabetes, and prevalence of microangiopathic complications prior to pregnancy (4,7,8,25). Like Murphy & al., we note that the median BMI, here above 25 kg/m2, increases progressively in T1D mothers who are now mostly overweight (7). Similarly, we note that the gold standard of therapeutic management during these pregnancies is now the subcutaneous insulin pump, since 60% of women have benefited from it. This is in line with recent data published by Stewart et al. (19). It is also worth noting that preconception HbA1c levels exceed the usual recommendations. Indeed, the American Diabetes Association recommends an HbA1c ≤ 6.5% (48 mmol/mol) before pregnancy, or < 6% (42 mmol/mol) in the absence of hypoglycemia (32). In our study only 23,9 % of women achieved this goal. This suggests a failure or non-compliance with preconception advice and pregnancy programming. However, publications have confirmed the impact of good pre-pregnancy metabolic and weight control on maternal-fetal morbidity, particularly on the risk of LGA (33–35).

The most frequently reported neonatal complications are prematurity, neonatal hypoglycemia and fetal overgrowth (macrosomia and LGA). In our study, we found a prematurity rate of 21.6%, which is lower than the 32.2% to 42,5% reported in the literature (7,25). However, most of these cohorts are either old (25), come from other countries (4,25,36) or include only a small number of T1D patients (4,36). Interestingly, our prematurity rate is of the same order of magnitude as in the recent series of 588 T1D pregnancies, also French, published by Lepercq et al. ; perhaps suggesting divergent obstetric practices between countries (37). The incidence of neonatal hypoglycemia was of 30.9% in our study, whereas in the literature it varies from 11.1% to 64% (25,37). There is no clear consensus on the definition of neonatal hypoglycemia, which explains the wide variability of results in the literature and their lack of comparability. Some have used a different biological definition with a threshold < 0.47g/L (4,25,36), others have considered only the first 3 hours of life (37) or only the first 24 hours of life (36). We have chosen a relatively strict definition of hypoglycemia, close to that of the Société Française de Néonatologie, possibly underestimating the reported rate (21). However, even with this definition, one third of newborns presented with hypoglycemia, which represents a much greater excess morbidity than in T2D or GD, where hypoglycemia rates are reported around 18% and 5% respectively (38). In our study, LGA multiplies the risk of neonatal hypoglycemia by 1.6, which is in line with the study by Yamamoto et al, where the risk is multiplied by 2.5 with a hypoglycemia rate, defined as blood glucose < 0.47 g/l, of 36.6% (12). Furthermore, accordingly to the study by Meek et al, involving 221 T1D pregnancies, we also observe that the risk of neonatal hypoglycemia was even higher above the 97^{th} percentile (OR 1.670 (CI 1.178 - 2.368)) (39). The incidence of respiratory distress was 8,4% in our study which is in line with the study by Meeks et al. (39). On the

contrary, Evers et al. found a much higher rate of respiratory distress (15%) but their cohort was older, contained more preterm birth (32.2%) and theses differences could be explained by the improvements in the immediate care of newborns, but also by the development of lung maturation antenatal corticosteroid therapy, thus reducing the risk of respiratory distress (25). In our study, the incidence of neonatal transfer was 12,4%, mostly represented by transfer in neonatal care (63,3%), whereas in the literature it varies from 19 to 47% (12,37). Again, our results are in line with those of the French study by Lepercq et al., suggesting divergent obstetric practices between countries (37).

There is currently no international or European consensus on the most appropriate growth charts during pregnancy in type 1 diabetes pregnancies. Very few studies have addressed this issue. Meek et al. have shown that the WHO growth standards, which do not take gestational age into account, are poorly suited to type 1 diabetes pregnancies given the prevalence of prematurity in this population. On the contrary, they reported that LGA, as defined by the GROW chart, which is the reference in the UK, and SGA, as defined by the INTERGROWTH chart, showed the strongest associations with neonatal complications (39). LGA was found in 52.8% of births in our study, which is consistent with the 41- 63% reported in the literature (4,37). Furthermore, the risk of neonatal complications in our study seemed more likely to occur in infants with the highest birth weights (≥ 4500g and ≥ 97^{th} percentile classes), in accordance with Meek et al. who also reported that infants > 97.7^{th} percentile had the highest risk of neonatal complications (39).

The most commonly cited underlying mechanism to explain maternal-fetal complications is maternal hyperglycemia during pregnancy and particularly in the third

trimester and days leading up to delivery (20). However, despite improvements in glycemic control during pregnancy, for example with continuous glucose monitoring (CGM) or, more recently, closed-loop insulin pumps, the risk of LGA and macrosomia remains high (19,40), suggesting that hyperglycemia may not be the only cause of excessive fetal weight gain. We therefore tried to identify other factors that might be predictive of neonatal complications, in particular among the maternal parameters. We found a rate of retinopathy of 25.8%, which is in line with the literature (7,41). On the other hand, the rate of pre-eclampsia was discreetly lower than in the literature, possibly due to the very regular follow-up by our specialist team (42,43). Finally, the rate of emergency caesarean section was similar to that reported in the literature. We found no significant increase in the risk of neonatal complications according to the duration of diabetes, the presence of retinopathy, which indirectly reflects the metabolic environment of the mother (41,44), and pre-eclampsia. On the contrary, Murphy et al. found a positive association between maternal characteristics such as diabetes duration and LGA (7). Furthermore, we observed an increased risk of neonatal complications in cases of emergency caesarean section. However, as LGA is a very common cause of caesarean section, the observed increased risk may be related to LGA rather than caesarean section itself.

Other maternal parameters would have been interesting to study, such as maternal weight gain during pregnancy or the type of treatment used. Indeed, in another work (*currently being published*), we were able to show that the more the woman was overweight during pregnancy, compared to the Institute of Medicine (IOM) recommendations according to her pregestational BMI, the more she presents a risk of LGA. Excess gestational weight gain could therefore be a confounding factor in the

risk of hypoglycemia, respiratory distress or even neonatal transfers. Different authors have reported this (11,12,30). Finally, there is the subject of ambulatory insulin pump, which has been reported by some to be associated with more LGA than multiple subcutaneous injections treatment (7).

Our study has several strengths: it is the largest cohort of pregnancies with type 1 diabetes monitored in the same hospital by a specialized medical and paramedical team, and it has similar characteristics to cohorts in the literature, giving it statistical power. In addition, our study contains a large number of both maternal and neonatal data on variables that are sometimes complex to study, such as neonatal hypoglycemia. However, given the retrospective nature of the study and its 25-year duration, some data are missing, which may lead to a lack of power. The monocentric nature of the study and the fact that it was carried out in a tertiary maternity hospital, which treats the highest-risk pregnancies in the northern region, may be responsible for a center effect, which may overestimate certain maternal and fetal complications. Finally, the low number of low birthweight babies (14 SGA and 13 ≤ 10^{th} percentile) compared with other birthweight categories prevented us from carrying out an analysis in this category. In addition, other potential limitations need to be discussed, notably the definition of neonatal hypoglycemia, which is far from a consensus in Europe and the rest of the world. Furthermore, we didn't have the maternal glycemia during birth, which is known to be predictive of fetal hypoglycemia.

CONCLUSION

In conclusion, our study suggests an increased risk of neonatal hypoglycemia and respiratory distress in children born to type 1 diabetic mothers with a birth weight

considered excessive. These risks do not appear to be increased by the duration of diabetes, the presence of retinopathy or the development of pre-eclampsia. Only cesarean section is associated with this neonatal morbidity but note that c-section is a reason for recourse in cases of LGA. Additional studies are necessary to identify independent influencing factors associated with neonatal morbidity with the aim of optimizing its prevention.

TABLES & FIGURES

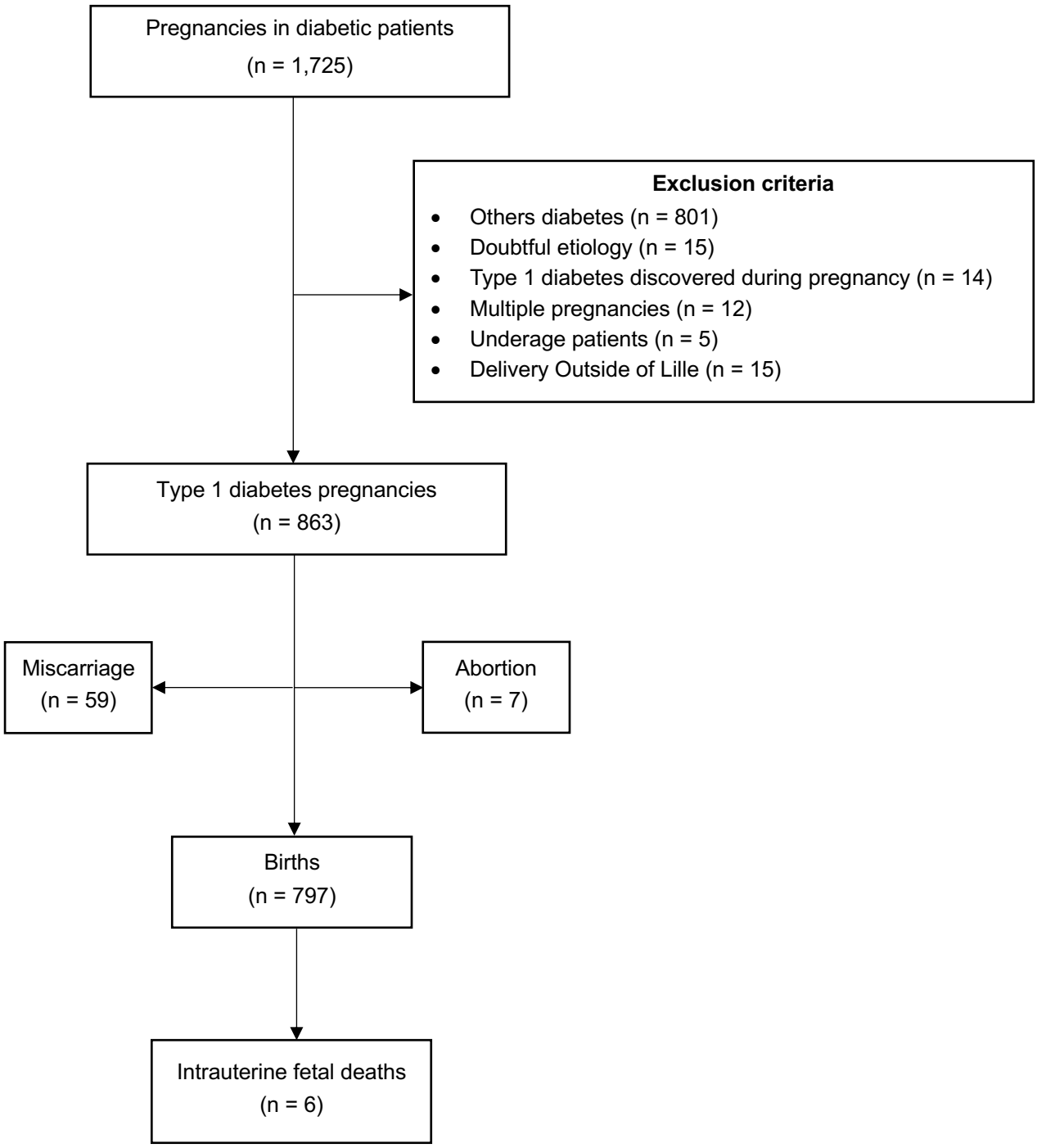


Figure 1: Patient enrolment flow chart

Maternal Characteristic		N
Age (years), mean ± SD	29.5 ± 4.9	797
BMI (kg/m^2), mean ± SD	25.0 ± 4.9	767
Nulliparity, n (%)	291 (36.6)	794
Smoking before pregnancy, n (%)	168 (27.0)	623
Smoking during pregnancy, n (%)	91 (15.2)	600
Duration of diabetes (years), mean ± SD	14.8 ± 7.9	795
< 5, n (%)	80 (10.1)	
5 – 10, n (%)	147 (18.5)	
10 – 20, n (%)	344 (43.3)	
≥ 20, n (%)	224 (28.2)	
Continuous subcutaneous insulin infusion, n (%)	475 (59.6)	797
FIT before pregnancy, n (%)	243 (30.5)	797
Pregestational HbA1c (%), mean ± SD	7.5 ± 1.5	719
No complication, n (%)	561 (70.7)	794
Diabetic retinopathy, n (%)	206 (25,8)	797
Diabetic nephropathy, n (%)	52 (6.5)	797
Hypertension, n (%)	27 (3.4)	797

Table 1: Baseline maternal characteristics

Abbreviations:
BMI: Body Mass Index
FIT: Functional Insulin Therapy
HbA1c: Glycosylated hemoglobin
SD: standard deviation

Newborn Characteristics		N
Sex (female/male), n (%)	392 (49.3)/403 (50.7)	795
Term (GA), mean ± SD	37.4 ± 2.0	795
Antenatal corticosteroid therapy, n (%)	128 (16.3)	784
Labor induction, n (%)	462 (76.6)	603
Vaginal Birth, n (%)	405 (50.8)	789
Birth Weight (g), mean ± SD	3520 ± 664.0	791
< 3000, n (%)	134 (16.9)	
3000 – 4000, n (%)	483 (61.1)	
4000 – 4500, n (%)	138 (17.4)	
≥ 4500, n (%)	36 (4.6)	
Birth Weight (percentile)		759
< 10^{th} percentile, n (%)	13 (1.7)	
10 – 90^{th} percentile, n (%)	345 (45.5)	
90 – 97^{th} percentile, n (%)	136 (17.9)	
≥ 97^{th} percentile, n (%)	265 (34.9)	
Birth Height (cm), mean ± SD	49.3 ± 2.4	746
Birth Cranial Perimeter (cm), mean ± SD	34.8 ± 1.9	760

Table 2: Newborn characteristics
Abbreviations:
GA: gestational age
SD: standard deviation

Maternal adverse outcomes		N
Diabetic retinopathy evolved, n (%)	187 (23.6)	794
Proteinuria evolved, n (%)	177 (22.3)	794
Gravid hypertension, n (%)	124 (15.6)	794
Preeclampsia, n (%)	87 (11.0)	794
Emergency caesarean section, n (%)	264 (33.1)	797
Postpartum hemorrhage, n (%)	84 (10.5)	797
Ketoacidosis during pregnancy, n (%)	23 (2.9)	797
Intensive Care Unit admission, n (%)	9 (1.1)	797
Fetal adverse outcomes		**N**
Prematurity, n (%)	172 (21.6)	795
Moderate Preterm, n (%)	146 (84.9)	
Very Preterm, n (%)	21 (12.1)	
Extremely Preterm, n (%)	5 (3.0)	
Macrosomia, n (%)	174 (22.0)	791
LGA, n (%)	401 (52.8)	759
SGA, n (%)	14 (1.8)	760
Apgar score < 7 at 1 min, n (%)	76 (9.6)	789
Apgar score < 7 at 5 min, n (%)	15 (1.9)	789
Arterial pH < 7.0, n (%)	17 (2.2)	757
Respiratory distress, n (%)	65 (8.4)	775
Intubation, n (%)	18 (28.1)	64
Hypoglycemia, n (%)	239 (30.9)	774
Perfusion, n (%)	102 (42.7)	239
Neonatal Transfer, n (%)	98 (12.4)	789
Resuscitation Ward, n (%)	36 (36.7)	98
IUFD, n (%)	6 (0.8)	795
Fetal composite criterion, n (%)	300 (38.5)	780

Table 3: Maternal and fetal adverse pregnancy outcomes

Abbreviations:

LGA: Large for Gestational Age according to AUDIPOG formula

SGA: Small for Gestational Age according to AUDIPOG formula

IUFD: Intra-Uterine Fetal Death

Fetal composite criterion: at least one the events among hypoglycemia, respiratory distress, neonatal transfer and IUFD

	Complication		Odds Ratio	p
	No	Yes	(CI 95%)	
Hypoglycemia				
Birth Weight Classes	N = 535	N = 239		**0.0288**
C1	89 (16.64)	39 (16.32)	0.759 (0.464 – 1.243)	0.2731
C2	339 (63.36)	136 (56.90)	1.000 (ref.)	-
C3	89 (16.64)	48 (20.08)	1.358 (0.906 – 2.037)	0.1387
C4	18 (3.36)	16 (6.69)	**2.263 (1.120 – 4.574)**	**0.0229**
Birth Weight Percentiles	N = 514	N = 230		**0.0166**
C1*	9 (1.75)	1 (0.43)	-	-
C2*	250 (48.64)	88 (38.26)	1.000 (ref.)	-
C3*	90 (17.51)	44 (19.13)	1.389 (0.899 – 2.145)	0.1768
C4*	165 (32.10)	97 (42.17)	**1.670 (1.178 – 2.368)**	**0.0338**
Respiratory distress				
Birth Weight Percentiles	N = 685	N = 60		**0.0019**
C1*	9 (1.31)	3 (5.00)	-	-
C2*	322 (47.01)	14 (23.33)	1.000 (ref.)	-
C3*	123 (17.96)	12 (20.00)	**2.244 (1.010 – 4.987)**	**0.0473**
C4*	231 (33.72)	31 (51.67)	**3.087 (1.606 – 5.932)**	**0.0007**
Neonatal Transfer				
Birth Weight Classes	N = 691	N = 98		**0.0242**
C1	86 (12.45)	48 (48.98)	1.955 (0.990 – 3.861)	0.0536
C2	451 (65.27)	32 (32.65)	1.000 (ref.)	-
C3	120 (17.37)	17 (17.35)	**2.462 (1.258 – 4.816)**	**0.0085**
C4	34 (4.92)	1 (1.02)	0.535 (0.070– 4.118)	0.5484
Birth Weight Percentiles	N = 665	N = 93		**< 0.0001**
C1*	9 (1.35)	4 (4.30)	-	-
C2*	321 (48.27)	23 (24.73)	1.000 (ref.)	-
C3*	121 (18.20)	15 (16.13)	1.730 (0.874 – 3.426)	0.1158
C4*	214 (32.18)	51 (54.84)	**3.326 (1.194 – 5.604)**	**< 0.0001**
Composite Criterion				
Birth Weight Classes	N = 390	N = 387		**0.0387**
C1	43 (11.03)	87 (22.48)	1.536 (0.975 – 2.421)	0.0642
C2	267 (68.46)	209 (54.01)	1.000 (ref.)	-
C3	67 (17.18)	69 (17.83)	1.340 (0.910 – 1.972)	0.1379
C4	13 (3.33)	22 (5.68)	**2.216 (1.086 – 4.522)**	**0.0287**
Birth Weight Percentiles	N = 380	N = 367		**0.0080**
C1*	6 (1.58)	5 (1.36)	-	-
C2*	193 (50.79)	145 (39.51)	1.000 (ref.)	-
C3*	68 (17.89)	67 (18.26)	1.311 (0.879 – 1.957)	0.1843
C4*	109 (29.74)	145 (40.87)	**1.767 (1.276 – 2.447)**	**0.0006**

Table 4: Birth weight according to birth weight classes/percentiles and fetal outcomes

Birth Weight Classes	Birth Weight Percentiles
C1 = < 3000 g	C1* = < 10^{th} percentile
C2 = 3000 – 4000 g	C2* = 10^{th} – 90^{th} percentile
C3 = 4000 – 4500 g	C3* = 90^{th} – 97^{th} percentile
C4 = ≥ 4500 g	C4* = ≥ 97^{th} percentile

Composite criterion: at least one the events among hypoglycemia, respiratory distress, neonatal transfer and IUFD

	Complication		Odds Ratio	p
	No	Yes	(CI 95%)	
Hypoglycemia				
Macrosomia	107 (20.00)	64 (26.78)	**1.579 (1.100 – 2.267)**	**0.0132**
LGA	255 (49.61)	141 (61.30)	**1.609 (1.172 – 2.209)**	**0.0032**
Respiratory distress				
Macrosomia	154 (21.69)	16 (24.62)	**2.190 (1.128 – 4.253)**	**0.0206**
LGA	369 (52.87)	45 (69.23)	**2.006 (1.161 – 3.468)**	**0.0127**
Neonatal Transfer				
Macrosomia	154 (22.29)	18 (18.37)	1.722 (0.923 – 3.213)	0.0874
LGA	358 (52.72)	61 (62.24)	1.478 (0.956 – 2.284)	0.0785
Composite Criterion				
Macrosomia	80 (20.51)	91 (23.51)	1.387 (0.979 – 1.964)	0.0656
LGA	181 (47.63)	217 (59.13)	**1.591 (1.191 – 2.125)**	**0.0017**

Table 5: Birth weight according to macrosomia/LGA and fetal outcomes

Abbreviations:

LGA : Large for Gestational Age

Composite criterion: at least one the events among hypoglycemia, respiratory distress, neonatal transfer and IUFD

	Complication		Odds Ratio	p
	No	Yes	(CI 95%)	
Hypoglycemia				
Duration of diabetes				0.0907
< 5 years	58 (10.86)	21 (8.82)	1.000 (ref.)	-
5 – 10 years	110 (20.60)	34 (14.29)	0.851 (0.451 – 1.604)	0.6179
10 – 20 years	216 (40.45)	113 (47.48)	1.468 (0.845 – 2.549)	0.1728
≥ 20 years	150 (28.09)	70 (29.41)	1.290 (0.724 – 2.297)	0.3881
Diabetic retinopathy	131 (24.49)	70 (29.29)	1.229 (0.871 – 1.734)	0.2402
Preeclampsia	53 (9.93)	31 (13.03)	1.174 (0.720 – 1.913)	0.5203
Emergency caesarean section	148 (27.66)	111 (46.44)	**2.154 (1.562 – 2.971)**	**< 0.0001**
Respiratory distress				
Duration of diabetes				0.0621
< 5 years	71 (10.01)	8 (12.50)	1.000 (ref.)	-
5 – 10 years	138 (19.46)	6 (9.38)	**0.244 (0.066 – 0.898)**	**0.0338**
10 – 20 years	297 (41.89)	33 (51.56)	1.031 (0.415 – 2.559)	0.9478
≥ 20 years	203 (28.63)	17 (26.56)	0.681 (0.2255 – 1.819)	0.4433
Diabetic retinopathy	185 (26.06)	16 (24.62)	0.627 (0.327 – 1.279)	0.2108
Preeclampsia	72 (10.17)	13 (20.00)	1.120 (0.523 – 2.399)	0.7701
Emergency caesarean section	224 (31.55)	36 (55.38)	**1.998 (1.129 – 3.537)**	**0.0175**
Neonatal Transfer				
Duration of diabetes				0.1882
< 5 years	71 (10.29)	9 (9.28)	1.000 (ref.)	-
5 – 10 years	135 (19.57)	12 (12.37)	0.512 (0.158 – 1.658)	0.2640
10 – 20 years	295 (42.75)	44 (45.36)	1.331 (0.525 – 3.371)	0.5468
≥ 20 years	189 (27.39)	32 (32.99)	1.313 (0.501 – 3.444)	0.5796
Diabetic retinopathy	174 (25.18)	30 (30.61)	0.930 (0.518 – 1.670)	0. 8092
Preeclampsia	65 (9.43)	21 (21.43)	1.038 (0.511 – 2.106)	0.9182
Emergency caesarean section	212 (30.68)	52 (53.06)	**1.702 (1.005 – 2.884)**	**0.0479**
Composite Criterion				
Duration of diabetes				0.1123
< 5 years	51 (10.63)	28 (9.40)	1.000 (ref.)	-
5 – 10 years	100 (20.83)	44 (14.77)	0.795 (0.430 – 2.064)	0.4641
10 – 20 years	194 (40.42)	137 (45.97)	1.355 (0.793 – 2.315)	0.2662
≥ 20 years	135 (28.13)	89 (29.87)	1.178 (0.672 – 2.297)	0.5672
Diabetic retinopathy	116 (24.17)	85 (28.33)	1.123 (0.795 – 1.587)	0.5100
Preeclampsia	40 (8.35)	45 (15.10)	1.215 (0.740 – 1.997)	0.4415
Emergency caesarean section	127 (26.46)	133 (44.33)	**1.915 (1.389 – 2.640)**	**< 0.0001**

Table 6: Maternal complications and fetal outcomes

IV. PERSPECTIVES

Notre étude a permis de mettre en évidence une association positive entre le poids de naissance et la survenue de complications néonatales chez les enfants nés de mères diabétiques de type 1. Nous avons en effet pu montrer un lien significatif entre l'excès de prise de poids fœtal et la survenue d'hypoglycémies néonatales ou de détresse respiratoire.

La surveillance de la croissance fœtale et la prévention de l'excès de prise de poids fœtal sont donc indispensables. Pour cela, il serait nécessaire d'identifier plus précisément les facteurs associés à l'apparition de cet excès de poids. En outre, plus de 50% des enfants étant au-delà du 90ème percentile, se pose la question de la pertinence des courbes de croissance fœtale usuelles au cours de la grossesse des patientes diabétiques de type 1. D'autres indicateurs pondéraux pouvant aider à mieux stratifier le risque associé à la macrosomie sembleraient intéressants.

Nous avons pu confirmer la prévalence excessive des hypoglycémies néonatales chez les enfants nés de mères diabétiques de type 1. Il n'existe pas à l'heure actuelle de consensus sur sa définition. Des études complémentaires sont donc nécessaires afin de déterminer des seuils diagnostiques et interventionnels pertinents en pratique clinique. De plus, suivre ces enfants sur le long terme afin de mieux en définir les conséquences serait d'intérêt.

En revanche, les paramètres maternels étudiés, à savoir la durée de diabète, la présence d'une rétinopathie diabétique ou le développement d'une prééclampsie, ne

sont pas apparus comme des facteurs prédictifs de la survenue de complications fœtales. Seule la réalisation d'une césarienne en urgence était associée à un risque accru d'hypoglycémies néonatales, de détresse respiratoire et de transfert néonatal. Ce résultat peut probablement être expliqué par le fait que le LGA est un motif très courant de recours à la césarienne. Des analyses multivariées complémentaires afin d'identifier des facteurs confondants sont donc nécessaires . Un ajustement sur la prise de poids maternelle au cours de la grossesse et sur l'utilisation de la pompe ambulatoire à insuline nous semble également pertinent à effectuer.

L'identification de l'ensemble des facteurs pouvant influencer la morbidité fœtale permettrait de mieux stratifier les risques de complications fœtales mais aussi de mieux les prévenir. La création d'un score de gravité néonatal, avec éventuelle pondération des complications les plus comorbides, pourrait permettre de proposer une prise en charge personnalisée à la fois des mères au cours de la grossesse mais aussi des enfants à la naissance.

V. CONCLUSION

L'excès de prise de poids fœtal au cours de la grossesse des femmes diabétiques de type 1 semble être un facteur de risque de morbidité néonatale et notamment d'hypoglycémies néonatales et de détresse respiratoire néonatale.

La surveillance de la croissance fœtale au cours de la grossesse ainsi que l'identification de facteurs maternels prédictifs de l'excès de prise de poids fœtal sont donc primordiales et repose sur une étroite collaboration entre le diabétologue, le gynécologue-obstétricien et la patiente.

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Date de soutenance : 16 octobre 2023

Titre de la thèse : Impact du poids de naissance sur la survenue de complications néonatales au cours de la grossesse de patientes diabétiques de type 1

Thèse - Médecine - Lille 2023

Cadre de classement : Diabétologie

DES : Endocrinologie - Diabétologie - Nutrition

Mots-clés : Diabète de type 1, Poids de naissance, Complications néonatales

Résumé :

Contexte et objectifs : Les complications materno-fœtales au cours des grossesses diabétiques de type 1 (DT1) demeurent supérieures à celles des patientes non diabétiques. L'excès de croissance fœtale (EPF) est l'une des complications fréquemment décrites et peut induire d'autres complications comme l'hypoglycémie néonatale ou la détresse respiratoire. Le but de cette étude était de déterminer l'impact du poids de naissance sur la survenue de complications néonatales au sein de cette population et d'en identifier les facteurs maternels prédictifs.

Matériel et méthode : Étude observationnelle, rétrospective, monocentrique menée au sein du CHU de Lille entre 1997 et 2022. Nous avons recueilli les données métaboliques maternelles, obstétricales ainsi que les données pédiatriques. Nous avons analysé les complications néonatales en fonction de catégories et de percentiles de poids de naissance. Un critère composite fœtal a été utilisé et était positif si au moins un des éléments suivants était présent : hypoglycémie néonatale, détresse respiratoire, transfert néonatal et mort fœtale in utéro. Les résultats sont exprimés en Odds Ratio (OR) avec leurs intervalles de confiance (IC) à 95%.

Résultats : 797 grossesses de patientes DT1 ont été analysées. Les mères avaient en moyenne un âge de 29.5 (± 4.9) ans, un IMC de 25 (± 4.9) kg/m² et 36,6% étaient nullipares. La durée moyenne de diabète était de 14.8 (± 7.9) années. L'HbA1c pré-gestationnelle moyenne était de 7,5 (± 1,5) % et la plupart des patientes (70,7%) présentaient un diabète non compliqué. Le terme moyen à la naissance était de 37,4 (± 2) semaines. Le poids de naissance moyen était de 3520 (± 664) grammes, avec 22% de macrosomes et 52,8% de LGA. 8,4 % des nouveau-nés ont présenté une détresse respiratoire, 30,9 % une hypoglycémie et 12,4 % ont dû être transférés. Le critère composite fœtal était présent chez plus d'un tiers des nouveau-nés (38,5%). Nous avons montré un risque significativement accru d'hypoglycémie (OR = 1,670 (IC 95 % = 1,178 à 2,368)), de détresse respiratoire (OR = 3.087 (CI 95% = 1.606 à 5.932)) et de transferts néonataux (OR = 3.326 (IC 95% = 1.194 à 5.604)) dans la classe C4* (≥ 97ème percentile). En revanche, nous n'avons pas montré d'augmentation significative du risque de complications néonatales en fonction de la durée de diabète, la présence d'une rétinopathie ou du développement d'une prééclampsie. Seule la césarienne était associée à ce risque.

Conclusion : L'EPF est associé aux hypoglycémies néonatales et à la détresse respiratoire néonatale. Ces résultats confirment l'importance de la surveillance de la croissance fœtale et de la prévention de l'excès de prise de poids fœtal. Cependant, les facteurs conduisant à cet EPF sont encore à identifier.

Composition du Jury :

Président : Pr Damien SUBTIL

Assesseurs : Pr Laurent STORME

Pr Anne VAMBERGUE

Directeur de thèse : Dr Madleen LEMAITRE