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Impact de l'IMC pré-gestationnel et de la prise de poids gestationnelle sur les complications materno-fœtales au cours de grossesses de patientes diabétiques de type 1

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Liste des abréviations

ADA : American Diabetes Association
BMI : Body Mass Index
CC : Composite Criterion, Critère Composite
CCf : Critère Composite fœtal
CCm : Critère Composite maternel
CHRU : Centre Hospitalier Régional Universitaire
CI : Confidence Interval
CNIL : Commission Nationale de l'Informatique et des Libertés
CSII : Continuous Subcutaneous Insulin Infusion
DT1 : Diabète de Type 1
ESHRE : European Society of Human Reproduction and Embryology
FIT : Functional Insulin Therapy
GWG : Gestational Weight Gain
HbA1c : hémoglobine glyquée
HTA : HyperTension Artérielle
ICU : Intensive Care Unit
IMC : Indice de Masse Corporelle
IOM : Institute Of Medecine
IQR : InterQuartile Range
IUFD : IntraUterine Fetal Death
LADA : Latent Autoimmune Diabetes in Adults
LGA : Large for Gestational Age
MODY : Maturity-Onset Diabetes of the Young
OMS : Organisation Mondiale de la Santé
OR : Odds Ratio
PPG : Prise de Poids Gestationnelle
RR : Risque Relatif
SD : Standard Deviation
SFD : Société Française de Diabétologie
SGA : Small for Gestational Age
T1D : Type 1 Diabetes
WHO : World Health Organization

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I. RÉSUMÉ

Contexte et objectif : À l'instar de l'augmentation de l'incidence du surpoids et de l'obésité, les patientes diabétiques de type 1 débutent leur grossesse de plus en plus fréquemment en condition de surcharge pondérale. L'excès pondéral préexistant à la grossesse et/ou per-partum est connu pour être un facteur de risque de survenue de nombreuses complications durant les grossesses de femmes non-diabétiques. De surcroit, l'équilibre métabolique est un enjeu majeur chez cette catégorie de patientes puisque son impact est démontré sur la morbidité materno-fœtale. Notre objectif était de définir les impacts respectifs de l'IMC (Indice de Masse Corporelle) pré-gestationnel et de l'excès de prise de poids gestationnelle (PPG) sur l'apparition de complications materno-fœtales au cours de grossesses de patientes diabétiques de type 1.

Matériel et méthodes : Étude observationnelle, rétrospective, monocentrique menée au sein de la maternité Jeanne de Flandres (CHRU, Lille). Nous avons recueilli les données métaboliques et les complications maternelles et fœtales chez l'ensemble des patientes diabétiques de type 1 enceintes suivies entre 1997 et 2021. Une première étude concerne l'analyse de l'IMC pré-gestationnel : classe 1 si IMC < 25 kg/m^2 (poids normal), classe 2 si IMC ≥ 25 et < 30 kg/m^2 (surpoids) et classe 3 si IMC ≥ 30 kg/m^2 (obésité). Une seconde étude analyse l'impact de la prise de poids au cours de la grossesse, en fonction de son adéquation avec les recommandations proposées par l'Institute of Medecine en 2009 : les grossesses sont réparties en catégorie WG (weight gain) -1 (PPG inférieure), WG 0 (PPG en adéquation), ou WG +1 (PPG supérieure). Nous avons défini un critère composite maternel (CCm), considéré positif si au moins un des éléments suivants était présent : rétinopathie diabétique, protéinurie, hypertension gravidique, prééclampsie, hémorragie du post-partum ou décompensation céto-acidosique. De la même manière, un critère composite fœtal (CCf) a été utilisé, considéré positif si au moins un des éléments suivants était présent : LGA, SGA, prématurité, dystocie des épaules, malformations congénitales, détresse respiratoire aiguë précoce ou transfert en réanimation néonatale. Les critères LGA, prématurité et prééclampsie ont également été analysés isolément dans la partie concernant l'IMC pré-gestationnel. Le critère LGA a été analysé isolément dans la partie concernant la PPG. Les résultats sont exprimés en Odds Ratio (OR) et leurs intervalles de confiance (CI) à 95%.

Résultats : Un total de 771 grossesses de diabétiques de type 1 a été analysé, dont 764 naissances vivantes. L'âge moyen était de 29.4 ± 4.9 ans, avec un IMC pré-gestationnel moyen à 24.85 ± 4.82 kg/m^2. 36.2% étaient nullipares. L'HbA1c médian pré-gestationnel était de 7.15 % (6.60 ; 8), avec une ancienneté médiane du diabète de 14 ans (8 ; 20). 70.4% des

patientes n'avaient pas de complications liées au diabète avant la grossesse. Les grossesses étaient marquées par la survenue de rétinopathie diabétique (26.7%), protéinurie (23.9%), HTA gravidique (17%) et prééclampsie (11.9%). La césarienne urgente et l'hémorragie du post-partum ont été comptabilisées toutes deux lors de 11% de l'ensemble des accouchements. Une décompensation céto-acidosique a été retrouvée lors de 9 grossesses (1.2%). Le terme médian était de 38 semaines d'aménorrhée (37 ; 38.4), avec un taux de prématurité de 21.5%. Le poids moyen à la naissance était de 3507 ± 678 grammes, avec un taux de LGA à 52.5%, de macrosomie à 22.8% et de SGA à 3%. 8.6% des accouchements étaient marqués par une dystocie des épaules. Parmi ces nouveau-nés, 7.9% présentaient des malformations congénitales, 9.6% une détresse respiratoire aiguë et 14.3% ont été transférés en réanimation néonatale. Les CCm et CCf étaient retrouvés respectivement dans 52.4% et 68.6% des grossesses.

Après répartition selon l'IMC pré-gestationnel, 62.1% des femmes étaient normopondérées (C1), 24.4% en surpoids (C2) et 13.5% obèses (C3). Le calcul des OR pour les critères composites, le critère LGA, prématurité et prééclampsie n'a pas montré de différence significative entre ces classes pondérales au sein de notre cohorte, malgré une tendance en faveur d'une augmentation du risque pour les classes C2 et C3.

Selon les recommandations de PPG, 18.3% des grossesses ont une PPG inférieure aux recommandations (WG -1), 31.1% ont une PPG correcte (WG 0) et 49.6% ont une PPG supérieure aux recommandations (WG +1). Pour le CCm, nous avons montré une différence significative entre WG +1 et WG 0 (référence), avec OR=1.44 [95% CI=1.03 to 2.01; p=0.033] avant ajustement, puis une disparition de cette significativité après ajustement : OR=1.40 [95% CI=0.98 to 2.01; p=0.06]. De même, pour le CCf, OR=1.45 [95% CI=1.02 to 2.07; p= 0.041] avant ajustement, puis OR=1.44 [95% CI=0.98 to 2.11; p=0.060] après ajustement. Le critère LGA était significativement lié à l'excès de PPG (WG +1), avec un OR=1.47 [95% CI=1.02 to 2.11; p=0.038] après ajustement.

Conclusion : L'excès de prise de poids gestationnelle au cours de grossesses de femmes diabétiques de type 1 semble être un facteur de risque plus important que l'IMC pré-gestationnel dans la survenue des complications materno-fœtales, appréciées sous la forme de nos critères composites. Ces résultats confirment l'importance de la surveillance pondérale au cours de ces grossesses à risque, dont l'enjeu concerne à la fois la santé de la future mère, le bon développement du fœtus puis la croissance du nouveau-né.

Mots-clés : Diabète de type 1, IMC pré-gestationnel, Gain de poids gestationnel, complications materno-fœtales

ABSTRACT:

Background and objective: As the incidence of overweight and obesity increases, type 1 diabetic patients are increasingly entering pregnancy in an overweight condition. Excess weight prior to pregnancy and/or per-partum is known to be a risk factor for many complications during pregnancies of non-diabetic women. Moreover, metabolic control is a major issue in this category of patients since its impact on maternal-fetal morbidity is demonstrated. Our objective was to define the respective impacts of pre-gestational BMI (Body Mass Index) and excess gestational weight gain (GWG) on the occurrence of maternal-fetal complications during pregnancies of type 1 diabetic patients.

Research design: Observational, retrospective, monocentric study conducted at the Jeanne de Flandres maternity hospital (CHRU, Lille). We collected metabolic data and maternal and fetal complications in all pregnant type 1 diabetic patients followed between 1997 and 2021. A first study concerns the analysis of pre-gestational BMI: class 1 if BMI < 25 kg/m^2 (normo weight), class 2 if BMI ≥ 25 and < 30 kg/m^2 (overweight) and class 3 if BMI ≥ 30 kg/m^2 (obesity). A second study analyzed the impact of weight gain during pregnancy, according to its adequacy with the recommendations proposed by the Institute of Medicine in 2009: pregnancies were divided into category WG (weight gain) -1 (lower GWG), WG 0 (GWG in adequacy), or WG +1 (higher GWG). We defined a maternal composite criterion (CCm), considered positive if at least one of the following elements was present: diabetic retinopathy, proteinuria, gravid hypertention, preeclampsia, postpartum hemorrhage, or ketoacidosis decompensation. Similarly, a fetal composite criterion (CCf) was used, considered positive if at least one of the following elements was present; LGA, SGA, prematurity, shoulder dystocia, congenital malformations, early acute respiratory distress, or transfer to neonatal intensive care unit. The criteria LGA, prematurity and preeclampsia were also analysed separately in the section on pre-gestational BMI, whereas only the LGA criterion was analysed separately in the section on GWG. The results are expressed as Odds Ratios (OR) and their 95% confidence intervals (CI).

Results: A total of 771 pregnancies of type 1 diabetics were analyzed, including 764 live births. The mean age was 29.4 ± 4.9 years, with a mean pre-gestational BMI of 24.85 ± 4.82 kg/m^2. 36.2% were nulliparous. The median pre-gestational HbA1c was 7.15% (6.60; 8), with a median age of diabetes of 14 years (8; 20). 70.4% of patients had no diabetes-related complications before pregnancy. The pregnancies were marked by the occurrence of diabetic retinopathy (26.7%), proteinuria (23.9%), gravidic hypertension (17%) and preeclampsia (11.9%). Urgent caesarean section and postpartum hemorrhage were both recorded in 11%

of all deliveries. Ketoacidosis decompensation was found in 9 pregnancies (1.2%). The median term was 38 weeks of amenorrhea (37; 38.4), with a prematurity rate of 21.5%. The mean birth weight was 3507 ± 678 grams, with a rate of LGA of 52.5%, macrosomia of 22.8% and SGA of 3%. 8.6% of deliveries were marked by shoulder dystocia. Among these newborns, 7.9% had congenital malformations, 9.6% had acute respiratory distress and 14.3% were transferred to neonatal care. Maternal and fetal CC were found in 52.4% and 68.6% of pregnancies respectively.

After distribution according to pre-gestational BMI, 62.1% of women were normo-weight (C1), 24.4% were overweight (C2) and 13.5% were obese (C3). Calculation of the ORs for the composite criteria and the LGA, prematurity and preeclampsia criteria showed no significant difference between these weight classes in our cohort, despite a trend toward increased risk for classes C2 and C3.

According to the GWG recommendations, 18.3% of pregnancies had a GWG lower than the recommendations (WG -1), 31.1% had a correct GWG (WG 0) and 49.6% had a GWG higher than the recommendations (WG +1). For the CCm, we showed a significant difference between WG +1 and WG 0 (reference), with OR=1.44 [95% CI=1.03 to 2.01; p=0.033] before adjustment, then a disappearance of this significance after adjustment: OR=1.40 [95% CI=0.98 to 2.01; p=0.06]. Similarly, for the CCf, OR=1.45 [95% CI=1.02 to 2.07; p=0.041] before adjustment, then OR=1.44 [95% CI=0.98 to 2.11; p=0.060] after adjustment. The LGA criterion was significantly related to excess GWG (WG +1), with an OR=1.47 [95% CI=1.02 to 2.11; p=0.038] after adjustment.

Conclusion: Excess GWG during pregnancies of type 1 diabetic women seems to be a more important risk factor than pre-gestational BMI in the occurrence of maternal-fetal complications, assessed in the form of our composite criteria. These results confirm the importance of weight monitoring during these high-risk pregnancies, which is important for the health of the mother-to-be, the proper development of the fetus and the growth of the newborn.

Key words: Type 1 diabetes, pregestational BMI, gestational weight gain, maternal-fetal morbidity

II. INTRODUCTION

1) Épidémiologie de la surcharge pondérale :

Le surpoids et l'obésité sont considérés comme une véritable pandémie du XXI^{ème} siècle. De 1980 à 2015, la prévalence de l'obésité a doublé dans plus de 70 pays industrialisés ou en voie de développement (1). L'incidence est d'ailleurs plus importante dans ces derniers, alors qu'elle stagne en Europe de l'Ouest (2). Concernant la population mondiale, en 2015, environ 39% des adultes avaient un IMC ≥ 25 kg/m^2 (quasiment 2 milliards d'individus), et environ 12% des adultes (plus de 600 millions) étaient obèses, avec un IMC ≥ 30 kg/m^2 (1,3). Les incidences ne cessent de s'accroître, particulièrement dans les pays en développement (2). Sur le plan national, en 2015, 37% des hommes et 27% des femmes françaises étaient en surpoids, et environ 17% des adultes étaient obèses (4), soit bien plus qu'en 1980 où le surpoids et l'obésité représentaient respectivement 26.8% et 6.3% des adultes français (5). Sur le plan local, la proportion d'obèse la plus importante parmi les départements français est retrouvée dans le Nord avec près d'un quart de la population adulte (25.6%) en situation d'obésité en 2016 (versus 12.8% en 1997), soit un doublement sur les 20 dernières années (6). L'incidence du surpoids/obésité est donc non négligeable et croissante au sein de la population féminine française, en âge de procréer (3), mais également chez les femmes diabétiques de type 1. D'ailleurs, en 2008, une étude comparant deux cohortes américaines (l'une incluant 333 femmes enceintes diabétiques de type 1 de 1978 à 1993, l'autre avec 358 femmes diabétiques de type 1 enceintes de 2002 à 2008) a montré une majoration significative du pourcentage de femmes DT1 en surpoids au début de leur grossesse, passant de 16.8% à 27.1% ($p<0.001$) entre la première et la seconde période (7).

2) Évaluation de la surcharge pondérale :

La mesure pondérale est effectuée par le calcul de l'Indice de Masse Corporelle (IMC), selon la formule Poids (kg) / Taille^2 (m). D'abord appelé « indice Quetelet de l'obésité », du nom du statisticien belge qui l'a créé en 1832, ce calcul est simple et reproductible. Il permet de définir des catégories pondérales, résumées par les recommandations de l'OMS (8) *:*

- *Insuffisance pondérale* si IMC < 18.5 kg/m^2
- *Corpulence normale* si IMC ≥ 18.5 kg/m^2 et < 25 kg/m^2
- *Surpoids* si IMC ≥ 25 kg/m^2 et < 30 kg/m^2
- *Obésité de grade 1* si IMC ≥ 30 kg/m^2 et < 35 kg/m^2
- *Obésité de grade 2* si IMC ≥ 35 kg/m^2 et < 40 kg/m^2
- *Obésité de grade 3* si IMC ≥ 40 kg/m^2

Le résultat du calcul de l'IMC ne permet pas de définir la composition corporelle, qui comporte la masse maigre (os, muscles, organes, liquides, soit 70 à 90% du poids du corps) et la masse grasse (tissu adipeux). Néanmoins, d'après les conclusions de Ancel Keys en 1972 (9), l'indice de Quetelet est la formule la plus fiable pour estimer la proportion de masse grasse, le renommant ainsi « indice de masse corporelle ». De plus, la formule n'intègre pas l'âge et le sexe, malgré leurs caractères confondants (10).

À ce jour, les techniques modernes permettant de mesurer précisément la quantité de masse grasse sont l'impédancemétrie et l'absorptiométrie biphotonique à rayons X (DEXA). Ces deux techniques sont coûteuses et peu accessibles, elles ne sont pas adaptées à une prise en charge standardisée au cours de la grossesse.

3) Surcharge pondérale et grossesse :

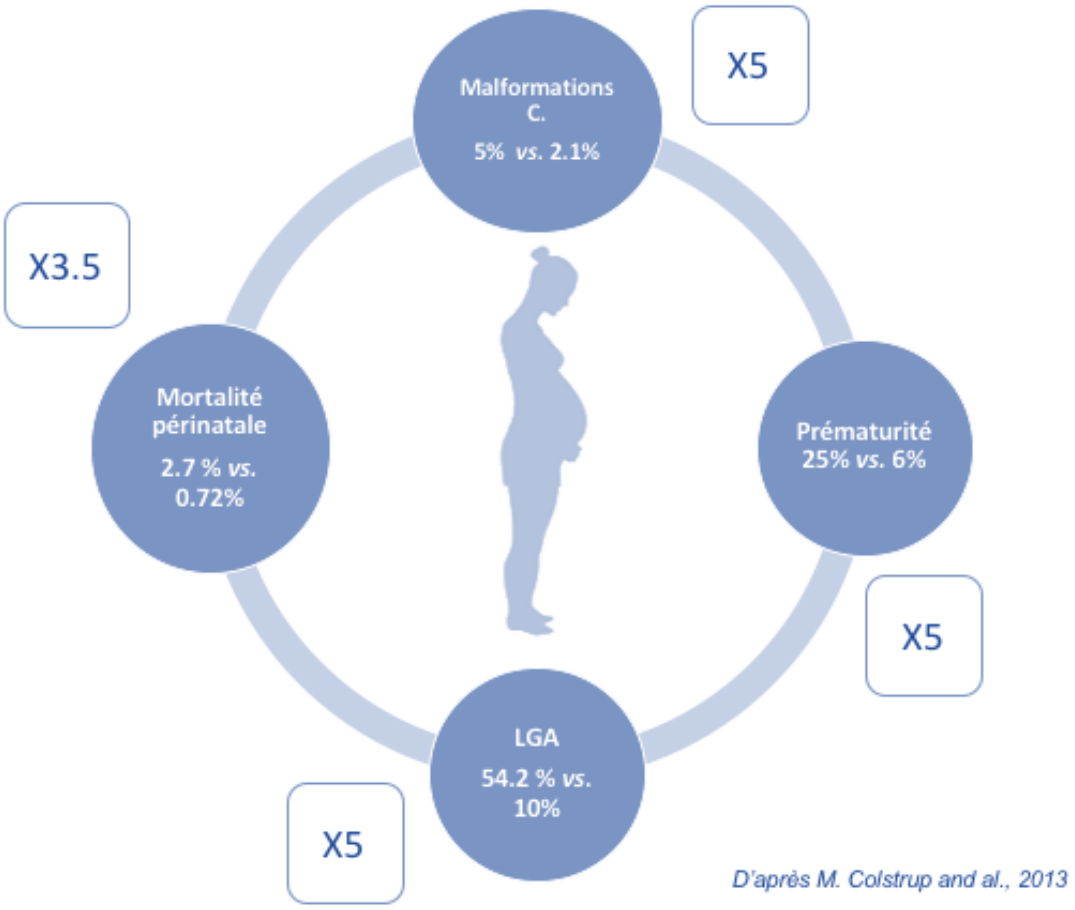
Les risques encourus lors d'une grossesse évoluant dans un contexte de surpoids ou d'obésité sont bien connus : prématurité (11), diabète gestationnel, prééclampsie, césarienne, excès de croissance fœtale, mauvaise adaptation à la vie extra-utérine (score d'Apgar bas) et fausse-couches. Il existe une corrélation positive entre l'IMC pré-gestationnel et la survenue de ces complications materno-fœtales (12). Leurs mécanismes physiopathologiques sont complexes (13), et impliquent un état pro-inflammatoire chronique, un excès de tissu adipeux qui, par ailleurs, est dysfonctionnel, causant notamment une diminution du taux d'adiponectine (une adipokine aux propriétés anti-inflammatoires), associé à des troubles du métabolisme lipidique, induisant une baisse de l'insulino-sensibilité (14), surajouté d'une dysfonction placentaire multifactorielle (15).

4) Diabète de type 1 et grossesse :

Le diabète au cours de la grossesse est marqué par un excès de morbi-mortalité en comparaison à la population générale. Cet excès est d'autant plus présent dans les diabètes pré-gestationnels qu'au cours du diabète gestationnel; avec des proportions divergentes des principales complications materno-fœtales entre le diabète de type 1 et le diabète de type 2. En 1989, la « Déclaration de St-Vincent »(16), après un travail conjoint par l'OMS, l'organisme européen International Diabetes Federation et les représentants de la santé de 22 pays d'Europe, a fixé un objectif d'amélioration de la qualité de vie des patients diabétiques, en réduisant l'incidence des complications induites par le diabète, notamment les complications materno-fœtales, avec une attention particulière portée sur l'éducation et la prévention.

L'amélioration de leur prise en charge globale avec un meilleur accès aux soins et aux assurances y était également préconisée. Pour les complications gestationnelles, l'objectif était d'atteindre le niveau d'incidence de la population générale.

Une méta-analyse publiée en 2013, incluant 14 099 femmes diabétiques de type 1, résume les 4 principales complications retrouvées en cas de grossesse, en comparaison aux grossesses non-diabétiques (17). Il est retrouvé un excès de croissance fœtale dans 54% des grossesses de diabétiques de type 1, contre 10% en l'absence de diabète (risque relatif (RR) = 4.5), la prématurité est retrouvée chez 25% des grossesses, contre 6% en l'absence de diabète (RR = 4.2), les malformations congénitales sont retrouvées dans 5% des grossesses, contre 2.1% en l'absence de diabète (RR = 2.4), et la mortalité périnatale, incluant les fausses-couches, est présente chez 2.7% des grossesses, contre 0.72% en population générale (RR = 3.7). Ces résultats montrent donc sans aucun doute que les objectifs de la déclaration de St-Vincent ne sont pas atteints. Notons aussi une majoration des autres risques périnataux : dystocie des épaules, souvent liée à la macrosomie, hypoglycémie néonatale, hypocalcémie néonatale et ictère néonatal (qui est le reflet de l'hyperbilirubinémie). De plus, la grossesse est également une période marquée par des risques accrus de complications métaboliques aigues : décompensation céto-acidosique (18), hypoglycémie maternelle, ou encore de



risques accrus pour les complications vasculaires chroniques : apparition/aggravation d'une rétinopathie (19), apparition/aggravation d'une néphropathie (20), qui peut mener à une prééclampsie si elle s'associe à une HTA gravidique.

Sur le plan physiopathologique, l'équilibre glycémique lors des premières semaines de grossesse est admis comme étant un déterminant de la survenue de fausses-couches (21) ou de malformations congénitales (22) en raison de son interaction avec l'organogenèse (23). L'excès de croissance fœtale est plutôt corrélé à l'équilibre métabolique en cours de grossesse (24). Dans une préalable étude réalisée dans notre centre, nous avions mis en évidence une association entre prématurité, césarienne et excès de croissance fœtale d'une part et équilibre métabolique apprécié par l'HbA1c du 1er mais également du 3e trimestre d'autre part (25). Il avait été montré que malgré une optimisation de l'équilibre glycémique au cours de la grossesse, la morbidité maternelle et fœtale restait supérieure à celle des femmes qui présentaient un équilibre métabolique idéal au cours de la grossesse, suggérant donc d'autres mécanismes d'implication. Le poids, définissant l'IMC pré-gestationnel, ou encore le gain de poids au cours de la grossesse pouvaient en effet être des facteurs confondants, qui n'avaient pas été pris en compte dans cette étude. En partant de cette constatation, il nous paraissait important d'étudier l'influence de ces paramètres sur la morbi-mortalité materno-fœtale au cours des grossesses de patientes diabétiques de type 1.

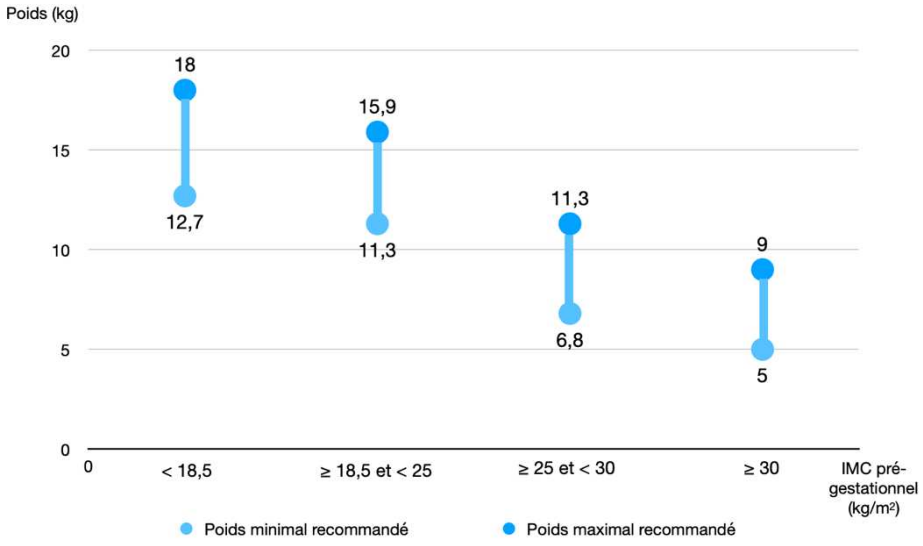
5) Surcharge pondérale, diabète de type 1 et grossesse :

Les risques encourus que ce soit en présence d'un diabète pré-gestationnel ou en situation de surpoids/obésité semblent similaires. Le potentiel effet synergique de ces deux facteurs sur la morbidité materno-fœtale est donc à appréhender. Le lien entre excès pondéral, diabète et grossesse a surtout été étudié pour le diabète gestationnel, ou pour des populations de « diabète pré-gestationnel », sans distinction entre type 1 et type 2. Néanmoins, depuis environ 20 ans, la littérature concernant spécifiquement les complications au cours des grossesses chez les diabétiques de type 1 en situation de surcharge pondérale, s'enrichit progressivement (26). Cependant, à notre connaissance, il n'y a pas d'étude française traitant cette problématique.

6) Bibliographie concernant le lien entre l'IMC pré-gestationnel, le diabète de type 1 et les complications materno-fœtales :

Articles s'intéressant à l'impact de l'IMC pré-gestationnel (PG)	Population étudiée Pays Date	Design	Principales données concernant les patientes diabétiques de type 1 (DT1)	Forces	Limites
Pre-pregnancy body mass index and the risk of adverse outcome in type 1 diabetic pregnancies: a population-based cohort study *Persson M. and al., 2012*	3457 grossesses DT1 764498 contrôles Suède 1998-2007	Registre national des naissances Multicentrique	Association linéaire significative entre un IMC PG > 25 kg/m² et la survenue de prééclampsie, malformations congénitales, césarienne, prématurité, macrosomie Risque de ces complications materno-fœtales largement supérieur à la population générale	-Première grande cohorte à démontrer les risques des grossesses de DT1 selon l'IMC PG avec un contrôle en population non diabétique -Recueil des données identique dans tous les centres	-Pas de donnée sur l'équilibre glycémique, l'ancienneté du diabète et les complications PG induites par le diabète -Exclusion des IMC PG < 18,5 kg/m², et des poids extrêmes (< 40 ou > 200 kg) -Automesure du poids PG
Prepregnancy Weight in Women with Type I Diabetes Mellitus: Effect on Pregnancy Outcomes *Kawakita T. and al., 2016*	426 grossesses DT1 États-Unis 1978-1995	Observationnel Rétrospectif Monocentrique	Augmentation du risque : • d'accouchement prématuré si IMC PG < 20 kg/m² • de césarienne urgente si IMC PG > 25 kg/m² Pas d'association significative entre la prééclampsie et l'IMC PG	La seule grande étude analysant des DT1 avant 2000	-Faible effectif des IMC PG ≥ 30 kg/m² (21 femmes) -HbA1 totale utilisée pour l'équilibre glycémique, moins précis que HbA1c -Automesure du poids PG
Maternal overweight and obesity and risk of pre-eclampsia in women with type 1 diabetes or type 2 diabetes *Persson M. and al., 2016*	7062 grossesses DT1 886 DT2 1509525 contrôles Suède 1997-2012	Registre national des naissances Multicentrique	Augmentation significative mais modeste du risque de prééclampsie en cas d'IMC PG > 30 kg/m²	-Très grande cohorte -Recueil des données identique dans tous les centres	-Pas de donnée sur l'équilibre glycémique, l'ancienneté du diabète et les complications PG induites par le diabète -Automesure du poids PG
Risks of asphyxia-related neonatal complications in offspring of mothers with type 1 or type 2 diabetes: the impact of maternal overweight and obesity *Cnattingius S. and al., 2017*	5941 grossesses DT1 711 DT2 1343751 contrôles Suède 1997-2012	Registre national des naissances Multicentrique	Augmentation linéaire significative du risque de score d'Apgar bas avec l'augmentation de l'IMC PG, sans différence significative avec les femmes non diabétiques	-Très grande cohorte -Recueil des données identique dans tous les centres	-Pas de donnée sur l'équilibre glycémique, l'ancienneté du diabète et les complications PG induites par le diabète. -Automesure du poids PG
Contemporary type 1 diabetes pregnancy outcomes: impact of obesity and glycaemic control *Abell SK. and al., 2016*	107 grossesses DT1 27075 contrôles Australie 2010-2013	Observationnel Rétrospectif Multicentrique	L'obésité maternelle est associée à une augmentation du risque de LGA et de malformations congénitales, pas pour la césarienne et la prématurité	Ajusté sur l'équilibre glycémique	- Pas de données sur l'équilibre glycémique pré-gestationnel et l'ancienneté du diabète -Faible effectif -Pas d'appariement avec le groupe contrôle
Maternal BMI and HDL as predictors of pregnancy outcome in women with type 1 diabetes *Ulmannova T. and al., 2014*	96 grossesses DT1 République tchèque 2003-2011	Observationnel Rétrospectif Monocentrique	La baisse d'1 point d'IMC augmente de 18% les chances du nouveau-né de naître sans aucune complication, pour une HbA1c fixe	Ajusté sur l'équilibre glycémique et la prise de poids gestationnelle	-Faible effectif -Intervalle d'IMC analysé : 22 à 35 kg/m²

7) Recommandations de prise de poids au cours de la grossesse :



Recommandations de prise de poids gestationnelle selon l'IOM

Les recommandations communément admises sont celles de l'Institute of Medecine (IOM) américain, réévaluées en 2009 (27). Ces recommandations indiquent un intervalle de prise de poids idéale lors d'une grossesse unique, en fonction de l'IMC pré-gestationnel, afin de limiter la survenue de complications néfastes pour la mère, comme la césarienne et la prise de poids en post-partum, ou pour son enfant, comme l'excès ou l'insuffisance de croissance fœtale et la prématurité (28). Aucune recommandation spécifique n'existe pour les diabétiques.

8) Excès de prise de poids gestationnelle et diabète de type 1 :

Depuis la fin du XX^{ème} siècle, de nombreuses études s'intéressent aux conséquences de l'excès de prise de poids gestationnelle (PPG) sur les complications maternelles et fœtales. Plus de 50% des grossesses non-diabétiques sont marquées par un excès de PPG (29), responsable d'un sur-risque de césarienne (29), de prééclampsie et de LGA (30). De même, on retrouve un excès de PPG chez presque 2/3 des grossesses de femmes diabétiques de type 1 (31). Parmi le peu de données disponibles concernant spécifiquement les complications, on retrouve des résultats contradictoires, notamment pour la prééclampsie (31,32). Néanmoins, la majorité des études est unanime sur le risque d'excès de croissance fœtale en cas d'excès de PPG chez les diabétiques de type 1 (7). Une altération de l'équilibre glycémique peut aussi survenir en cas d'excès de PPG, en lien avec l'augmentation de l'insulino-résistance, et peut donc participer à la genèse de ces complications. Les femmes qui présentent une PPG insuffisante présentent, quant à elle, plus de risque d'accoucher prématurément et/ou d'avoir un nouveau-né hypotrophe (29).

9) Bibliographie concernant le lien entre la prise de poids gestationnelle, le diabète de type 1 et les complications materno-fœtales :

Articles s'intéressant à l'impact de l'excès de prise de poids gestationnelle (PPG)	Population étudiée Pays Date	Design	Principales données concernant les patientes diabétiques de type 1 (DT1)	Forces	Limites
Effect of excess gestational weight gain on pregnancy outcomes in women with type 1 diabetes *Scifres CM. and al., 2014*	175 grossesses DT1 États-Unis 2009-2012	Observationnel Rétrospectif Monocentrique	Association significative entre l'excès de PPG et un fœtus LGA/macrosome, quel que soit l'IMC PG Pas d'association significative avec la césarienne, la prééclampsie, les malformations néonatales, l'hypoglycémie néonatale, la dystocie des épaules…	- Première étude s'intéressant exclusivement à la PPG chez les DT1 -Ajustement sur l'HbA1c, l'âge maternel, la parité, l'IMC PG, la présence de complications vasculaires -Large panel de complications	-Faible effectif -Peu d'IMC bas ou PPG insuffisant
Outcomes of type 1 diabetes mellitus in pregnancy; effect of excessive gestational weight gain and hyperglycaemia on fetal growth *Mohammed Bashir M. and al., 2018*	110 grossesses DT1 1419 contrôles Qatar 2015-2016	Observationnel Rétrospectif Monocentrique	Augmentation significative du risque de LGA en cas d'excès de PPG Mais pas pour macrosomie, prématurité, césarienne ou hypoglycémie néonatale	-Ajustement sur l'âge maternel, l'IMC PG et l'HbA1c aux 1er et 3ème trimestres	-Faible effectif -Peu de donnée sur la PPG au 3ème trimestre
Characterizing Gestational Weight Gain According to Institute of Medicine Guidelines in Women with Type 1 Diabetes Mellitus: Association with Maternal and Perinatal Outcome *Kawakita T. and al., 2016*	293 grossesses DT1 États-Unis 1978-1995	2ème analyse d'une cohorte multicentrique issue d'un essai thérapeutique randomisé sur les effets d'un contrôle glycémique strict par rapport au contrôle glycémique habituel sur le taux de malformations congénitales majeures	Association significative entre l'excès de PPG et la macrosomie et l'ictère néonatale Mais pas pour la césarienne, le score d'Apgar < 7, la prématurité, …	-Ajustement sur l'âge maternel, la parité, l'IMC PG, l'HbA1c au 2ème trimestre et à l'accouchement, les complications vasculaires, les antécédents de césarienne et l'HTA chronique -large panel de complications	-Recommandations sur la PPG différentes à l'époque - Possible prise de poids majorée en cas d'intensification de l'insulinothérapie dans le bras « contrôle glycémique strict » -HbA1 totale utilisée pour l'équilibre glycémique, moins précis que HbA1c
Impact of gestational weight gain and prepregnancy body mass index on the prevalence of large-for-gestational age infants in two cohorts of women with type 1 insulin-dependent diabetes: a cross-sectional population study *McWhorter KL. and al., 2018*	Cohorte 1 : 333 grossesses DT1 (1978-1993) Cohorte 2 : 358 grossesses DT1 (2002-2008) États-Unis	Observationnel Rétrospectif Multicentrique	Augmentation significative du risque de LGA en cas d'IMC PG > 25 kg/m² et excès de PPG dans les deux cohortes, en comparaison avec les femmes à IMC PG normal et PPG correcte	Ajustement sur l'âge maternel, la parité, l'IMC PG et la survenue de prééclampsie	-Pas de donnée sur l'équilibre glycémique, l'ancienneté du diabète et la présence de complications vasculaires PG -Recommandations sur la PPG différentes à l'époque
Determinants of preeclampsia in women with type 1 diabetes *Gutaj P. and al., 2017*	165 grossesses DT1 Pologne 2012-2014	Observationnel Prospectif Monocentrique	Augmentation modérée du risque de prééclampsie si excès de PPG	-Ajusté sur l'IMC du 1er trimestre -Design prospectif et monocentrique	-Faible effectif -Peu d'IMC ≥ 25 kg/m² (45 patientes)
Higher gestational weight gain is associated with increasing offspring birth weight independent of maternal glycemic control in women with type 1 diabetes *Secher AL. and al., 2014*	115 grossesses DT1 Danemark 2009-2011	Observationnel Rétrospectif Monocentrique	La PPG est associé positivement au poids de naissance, indépendamment de l'IMC PG et de l'équilibre glycémique en fin de grossesse	-Ajusté sur l'IMC PG, l'HbA1c au 3ème trimestre, le tabac et la parité -Exclusion de néphropathie diabétique, prééclampsie et prématurité	-Faible effectif -Automesure du poids PG -Meilleur équilibre glycémique et moins de complications à l'inclusion en comparaison aux autres études

10) Objectifs de l'étude :

Les grossesses des femmes diabétiques de type 1 sont donc des grossesses à risque, pouvant avoir des conséquences sur la santé de la mère, entraver le bon développement du fœtus mais également la croissance du nouveau-né. À l'instar de la population mondiale, les femmes diabétiques de type 1 présentent une augmentation progressive de leur IMC pré-conceptionnel. Les complications en lien avec l'association surcharge pondérale et grossesse sont décrites depuis peu pour le diabète de type 1, et sont parfois contradictoires.

De plus, la plupart de ces études s'intéressent aux complications principales, telles que la prééclampsie, la césarienne, la prématurité et l'excès de croissance fœtale. Il y a peu de données concernant d'autres complications pertinentes maternelles comme l'aggravation de la microangiopathie, l'hémorragie du post-partum et la décompensation céto-acidosique, ou chez le nouveau-né : la dystocie des épaules, une anomalie du score d'Apgar, une acidose néonatale ou encore une détresse respiratoire aiguë.

Le but de cette étude est de déterminer l'impact de l'IMC pré-gestationnel et de l'excès de gain de poids gestationnel sur les complications materno-fœtales au cours de grossesses de patientes diabétiques de type 1. Identifier les risques encourus par les femmes présentant l'association diabète de type 1 et problématique pondérale lors de leur grossesse pourrait permettre de mieux prévenir la survenue de ces complications et d'individualiser la prise en charge des femmes les plus à risque.

Pour se faire, nous avons recensé l'ensemble des patientes diabétiques de type 1 enceintes qui ont été suivies au sein de la structure Diabète & Grossesse entre 1997 et 2021. Ces patientes devaient être insulino-traitées au moment de la conception et avoir été suivies jusqu'à leur accouchement au sein de notre structure.

Nous avons exclu les patientes présentant un autre type de diabète (type 1 lent non insulino-traitée, monogénique, type 2 ou pour lesquelles un doute diagnostic persistait), celles dont le diagnostic de diabète de type 1 a été effectué après la date de début de grossesse, les grossesses gémellaires ou triples, les patientes mineures et celles qui ont arrêté leur suivi avant l'accouchement ou qui n'ont pas accouché au sein du CHRU.

Ainsi, nous avons recueilli et analysé les données de 831 grossesses de 549 patientes diabétiques de type 1. L'ensemble des résultats est rapporté dans les articles scientifiques suivants :

III. Premier article :

Est-ce que le surpoids ou l'obésité maternels ont un impact sur la survenue de complications materno-fœtales au cours de grossesses de patientes diabétiques de type 1 ?

First article:

Does maternal overweight or obesity have an impact on maternal-fetal complications in type 1 diabetes pregnancies?

1) INTRODUCTION:

Overweight and obesity are considered the greatest pandemic of the 21st century. From 1980 to 2015, the prevalence of obesity doubled in more than 70 industrialized and developing countries (1). The incidence is higher in the latter, while it is stagnant in Western Europe (2). In 2015, about 39% of adults, or nearly 2 billion people, had a BMI ≥ 25 kg/m^2 and about 12% of adults, or more than 600 million, were obese with a BMI ≥ 30 kg/m^2 (1,3). France is no exception to this trend. In 2015, 37% of French men and 27% of French women were overweight, and about 17% of adults were obese (4), whereas in 1980, overweight and obesity affected only 26.8% and 6.3% of French adults, respectively (5). The Nord department is marked by almost a quarter of the adult population being obese in 2016 (25.6%), compared to 12.8% in 1997, i.e., double in almost 20 years (6).

The trend towards Increased weight also applies to women of childbearing age (3). A study published in 2008, comparing two American cohorts of type 1 diabetics (one with 333 pre-pregnant type 1 diabetics from 1978 to 1993, the other with 358 pregnant type 1 diabetics from 2002 to 2008) showed a significant increase in the percentage of women who were overweight at the beginning of their pregnancy, from 16.8% to 27.1% ($p<0.001$) (7). Similarly, an increase in pregestational BMI was shown by the study of 881 type 1 diabetic women: in the period 1989-1992, they had 19.4% overweight and 1.8% obese women, with a mean BMI of 23.1 kg/m2, whereas in the period 2004-2008, their proportion increased to 32.8% and 9.8%, respectively, with a mean BMI of 24.8 kg/m2 ($p<0.001$) (25).

Furthermore, pregestational diabetes is marked by an excess of morbidity compared to the general population. This excess morbidity persists despite the “Saint Vincent Declaration” (16), published in 1989 after a joint effort by WHO, the International Diabetes Federation and health representatives from 22 European countries. Its objective was to improve the quality of life of diabetic patients by reducing the incidence of diabetes-induced complications, especially maternal-fetal ones, with an emphasis on education and prevention, in order to reach the incidence level of the general population. A meta-analysis published in 2013, including 14099 women with type 1 diabetes, highlighted the main complications found in diabetic pregnancies (17) : fetal growth excess (54% of pregnancies with type 1 diabetes, versus 10% without diabetes (relative risk (RR) = 4.5)), prematurity (25% of pregnancies, versus 6% without diabetes (RR = 4. 2)), congenital malformations (5% of pregnancies, versus 2.1% without diabetes (RR = 2.4)), and perinatal mortality, including miscarriage (2.7% of pregnancies,

versus 0.72% in the general population (RR = 3.7)). We can also add the risks of shoulder dystocia, often linked to macrosomia, neonatal hypoglycemia, neonatal hypocalcemia and neonatal jaundice (reflecting hyperbilirubinemia). In addition, pregnancies are also marked by metabolic complications of diabetes: ketoacidosis decompensation (18), hypoglycemia, or vascular complications: retinopathy (19), nephropathy (20) and preeclampsia if associated with gestational hypertension.

Clearly, metabolic imbalance is one of the main mechanisms leading to complications. Glycemic control in the early weeks of pregnancy is known to be a determinant of miscarriage (13) or congenital malformations (14) because of its interaction with organogenesis (15). Fetal overgrowth is rather correlated with the average glycemic control during pregnancy (16). In a recent study, performed in our center, we found that the occurrence of prematurity, caesarean section or fetal overgrowth was associated with the HbA1c of the first but also the third trimester (17). Similarly, despite correction of glycemic imbalance in the first trimester, maternal and fetal morbidity remains high at term, suggesting other mechanisms of involvement. Weight seems to be a confounding factor, which is not always considered in studies.

Pregnancies of overweight and obese patients are marked by additional risks such as prematurity (18), preeclampsia, caesarean section, fetal overgrowth or even macrosomia, poor adaptation to extrauterine life (low Apgar score) and miscarriage (19). A potential synergistic effect of weight and diabetes needs to be studied. Over the last 20 years, many authors have studied the unfavorable evolution of pregnancy in overweight type 1 diabetics. On the other hand, few data exist concerning other relevant complications, especially neonatal ones, such as shoulder dystocia, low Apgar score, neonatal acidosis and acute respiratory distress, or worsening of microangiopathy, postpartum hemorrhage and ketoacidosis.

Based on the observation that good glycemic control is not sufficient to prevent the occurrence of these complications, the aim of this study is to determine the impact of pregestational BMI on maternal-fetal complications in pregnancies of patients with type 1 diabetes. Identifying the risks incurred by overweight or obese type 1 diabetic women during pregnancy could allow better individualized prevention of these complications.

2) RESEARCH DESIGN:

This observational, retrospective, single-center study took place in tertiary care center named Jeanne de Flandres Hospital, University Hospital of Lille, France. All maternal characteristics, obstetrical follow-up, the course of delivery and the characteristics of the newborn were

collected from computerized or archived records. Follow-up methods have not changed since 1997: patients are seen in consultation or in daily hospital, and they are called regularly by specialized nurses. Obstetrical and diabetes follow-up was made according to the recommendations of the SFD (Société Francophone de Diabétologie) (33) and the ADA (American Diabetes Association) (34). Patients were informed of the possibility of future use of their personal data for research purposes. The database was declared to the CNIL (Commision Nationale de l'Informatique et des Libertés), and the data were anonymized.

Only pregnant women with type 1 diabetes, consulting the Diabetes and Pregnancy structure between 1997 and 2021, and followed until their delivery in our hospital, were included. Patients with another type of diabetes (LADA (Latent Autoimmune Diabetes in Adults), type 2 diabetes, MODY (Maturity-Onset Diabetes of the Young), secondary diabetes or with persistent etiological doubt), type 1 diabetes diagnosed after the beginning of the pregnancy, twin or multiple pregnancies, minor, and those who stopped their follow-up before delivery or who did not deliver in our maternity were excluded from the following analysis.

Data collection:

Maternal characteristics: demographic, metabolic, diabetic history (duration, treatment, vascular complications) were collected during a preconception consultation in the case of a planned pregnancy, or during the first consultation after the diagnosis of the pregnancy in the opposite case. A mixed follow-up was carried out monthly until the 6^{th} month: regular consultations and then a biweekly telephone call by specialized nurses for weight, metabolic monitoring and adjustment of insulin titrations, then during the day hospital for obstetrical follow-up associated with biweekly phone calls. Multi-daily monitoring blood glucose was carried out with consensus targets: fasting < 95 mg/dL and 2 hours after the start of a meal < 120 mg/dL. Glycemic targets and follow-up were in accordance with SFD recommendations. Delivery reports were consulted to collect delivery data and newborn characteristics.

Regarding anthropometric data, pregestational weight and height were used to calculate Body Mass Index (BMI=kilograms/meter^2). Smoking was checked before pregnancy, and if it existed, it was regularly asked if it had been stopped. Obstetrical history was noted: gravidity, parity, gestational age, history of macrosomia, gestational hypertension, preeclampsia, miscarriage, or intrauterine fetal death (IUFD).

Regarding pregestational BMI, 3 classes were defined: class 1 = BMI < 25 kg/m^2 ("normo-weighted"), class 2 = BMI ≥ 25 and < 30 kg/m^2 ("overweight"), and class 3 = BMI ≥ 30 kg/m^2 ("obesity"), according to WHO criteria (8). We decided to include patients with low BMI (i.e.,

BMI < 18.5 kg/m^2) in the "normo-weighted" class because of the insufficient number of low BMI patients in our cohort. In addition, a dietary survey was performed by experienced dieticians at the beginning of pregnancy management, adjusted according to glycemic control, and reinforced in case of excessive weight gain.

Regarding the characteristics of diabetes, we collected the date of diabetes diagnosis, the type of insulin therapy (either short-acting insulin analogue before meals and a long-acting insulin analogue injection, or continuous subcutaneous insulin infusion (CSII)), the pre-gestational HbA1c, which is the last known value before the diagnosis of pregnancy, and the per-partum HbA1c measured every trimester.

Regarding vascular complications of diabetes, we looked for arterial hypertension, defined as blood pressure > 140/90 mmHg measured at 2 different visits or the use of antihypertensive treatment; diabetic nephropathy, defined as albuminuria ≥ 30 mg/24h or chronic renal failure; and diabetic retinopathy, defined as abnormal fundus examination.

Concerning the complications of diabetes during pregnancy, we noted the appearance or worsening of retinopathy (a fundus was performed every 3 months), the appearance or worsening of nephropathy or gravidic hypertension (sought monthly). In addition, cases of preeclampsia (defined by the appearance or concomitant worsening of proteinuria ≥ 300 mg/24h and gravidic hypertension after 20 amenorrhea weeks), ketoacidosis, and maternal transfer to an intensive care unit (ICU) were reported.

Concerning the obstetrical characteristics and complications, we collected the delivery term, preterm births (delivery before 37 amenorrhea weeks), the delivery mode (vaginal or caesarean section), and we specified the conditions of its realization. In the case of a vaginal delivery, we have collected more precision: the artificial induction of labor, the instrumental using (forceps or vacuum-assisted delivery), the occurrence of cervical dystocia (defined as the prolonged non-progression of labor due to insufficient dilation of the cervix, despite uterine contractions), or a shoulder dystocia (defined as the difficulty for fetal extraction after the exit of the head, due to a blockage of at least one shoulder above the superior strait), and in the case of a cesarean section if it was an urgent realization before labor. We also reported the occurrence of post-partum hemorrhage (defined as bleeding > 500 ml when vaginal delivery, or > 1000 ml when cesarean delivery, occurring within 24 hours of delivery). Finally, we counted miscarriages and IUFD (< 22 and ≥ 22 amenorrhea weeks, respectively, according to ESHRE recommendations) (35). Thus, we defined one maternal composite criterion, which is composed by the appearance or aggravation of retinopathy, proteinuria, gravidic hypertension,

preeclampsia, post-partum hemorrhage or ketoacidosis decompensation. This criterion was positive if at least one of the elements was present.

Regarding the newborn characteristics, we reported sex, birth weight to define macrosomia (birth weight ≥ 4000 g), Large for Gestational Age (LGA) or Small for Gestational Age (SGA) according to the Audipog formula (respectively birth weight > 90^{th} or < 10^{th} percentile, including term, birth weight, and sex). We indicated the arterial pH on umbilical cord blood gas analysis, and Apgar score at 1 and 5 minutes of life, while specifying the cases of arterial pH < 7 (defining a severe neonatal acidosis), and the cases of Apgar score < 7 (corresponding to an immediate bad adaptation to the extrauterine life). We also identified severe malformations (defined as malformations leading to death or transfer to intensive care within the first 2 days of life or having a major functional impact for the newborn). Finally, the occurrence of acute respiratory distress (defined as the need for high-flow oxygen therapy or intubation during the first hour of life) and transfer to neonatal ICU were collected. Similarly, we defined a fetal composite criterion, composed of prematurity, shoulder dystocia, severe malformations, respiratory distress or neonatal ICU admission, LGA and SGA. This criterion is positive if at least one of the elements is present.

Statistical analyses:

Statistical analyses were conducted using SAS software (SAS Institute 9.4, Cary, USA). Categorical variables were reported as numbers (percentage). Quantitative variables were described by means ± standard deviation, in case of Gaussian distribution, or otherwise by median (interquartile range (IQR)). Normality of numerical variables was checked graphically and tested using the Shapiro-Wilk test.

Five pregnancy outcomes were investigated: preeclampsia, maternal composite criterion, LGA, prematurity and fetal composite criterion. We assessed the association of BMI (in kg/m²) with pregnancy outcomes using logistic regression models before and after adjustment on predefined confounding factors (HbA1c, year of delivery, type of treatment). Comparisons between the three classes of BMI were made using logistical regression models before and after adjustment on predefined confounding factors, using class 1 as reference. We examined the log-linearity assumption for continuous features using restricted cubic spline functions. All results were expressed in odds ratios (OR) and their 95% confidence intervals (CI). To avoid bias, multiple imputations using the multivariate imputation by chained equations methodology were applied to account for missing data. The results of each imputed dataset were pooled using Rubin's rules. Statistical testing was done at the 2-tailed level of 0.05.

3) RESULTS:

Demographics characteristics of type 1 pregestational diabetes women:

A total of 1651 pregnancies of women with pregestational diabetes were identified, of which 820 had one of the exclusion criteria: 778 pregnancies with another diagnosis than type 1 (type 2, MODY, LADA, secondary) or a persistent diagnostic doubt, 14 discoveries of type 1 diabetes after the beginning of the pregnancy, 13 patients lost to follow-up before delivery or who did not deliver in our maternity hospital, 10 twins or multiples pregnancies and 5 pregnancies in underage patients. Thus, we constituted a pool of 831 pregnancies from 549 type 1 diabetes patients. We excluded 60 miscarriages and 7 IUFD (i.e., 7.2% and 0.8% of all pregnancies, respectively). Therefore, our cohort is composed of 764 alive births. There was 334 women with 1 pregnancy, 155 with 2 pregnancies and 60 with 3 pregnancies or more during the studied period (*Figure 1)*.

Baseline maternal characteristics

These characteristics are presented in *Table 1*. To compensate the lack of data for some values, we present the results after multiple imputation. The patients were 29.4 (± 4.9) years old, their pregestational BMI was 24.85 ± 4.82 kg/m^2. 171 (28.3%) of them smoked before pregnancy, and 95 (16.4%) were still smoking during pregnancy. The median diabetes duration was 14 (IQR, 8 to 20) years. CSII was used in 456 (59.1%) pregnancies and 228 (29.6%) patients were practicing FIT (Functional Insulin Therapy). Regarding pregestational glycemic control, median HbA1c was 7.15 % (54.6 mmol/mol) (IQR, 6.60 to 8), with 126 (18.3%) of women having an HbA1c < 6.5 % (47.5 mmol/mol), which is the pregestational goal according to the ADA recommendations. Most included patients (541, 70.4%) had no linked diabetes complication prior to pregnancy, while diabetic retinopathy was present in 200 (25.9%) women, diabetic nephropathy in 54 (7%) and hypertension in 30 (3.9%). 279 (36.2%) patients were nulliparous.

Adverse maternal outcomes during pregnancies in T1D:

Table 2 shows the adverse maternal and fetal outcomes. To compensate the lack of data for some values, we present the results after multiple imputation. The mean HbA1c during pregnancy was 6.47 % (47.2 mmol/mol) (IQR, 6.03 to 6.97). The onset or worsening of retinopathy, proteinuria or gestational hypertension was found in 206 (26.7%), 184 (23.9%)

and 131 (17%) women respectively. In addition, 92 (11.9%) women had preeclampsia. Half of the deliveries (50.8%) were performed vaginally, of which 285 (74.6%) were induced. An emergency or scheduled caesarean section was performed in 49.2% of patients, while an emergency caesarean section before labour in 84 (11%) of all pregnancies. Postpartum hemorrhage was recorded in 85 (11%) pregnancies. Less frequently, we counted a ketoacidosis decompensation or a transfer to ICU in 24 (3.1%) and 9 (1.2%) pregnancies respectively. Finally, the maternal criterion was found in 52.4% (404) of patients.

Fetal characteristics and outcomes, all weights combined:

The mean gestational age at delivery was 38 (IQR, 37 to 38.4) amenorrhea weeks, with 166 (21.5%) preterm births. Birth weight was 3507 (± 678 grams). The rate of macrosomia was 22.8% (173), LGA was 52.5% (405) and SGA was 3% (23), according to the Audipog formula. Severe malformations concerned 61 (7.9%) newborns. 66 (8.6%) deliveries were marked by shoulder dystocia, the Apgar score was < 7 at 1 and 5 minutes respectively in 68 (9.8%) and 19 (2.7%) births. Arterial pH was < 7.15 in 24.5% and < 7 in 2.4% of births. Respiratory distress in the first hours of life occurred in 74 (9.6%) births, and 110 (14.3%) newborns were transferred to neonatal ICU. Finally, the fetal composite criterion was found in 68.6% (529) cases *(Table 2).*

Pregestational BMI and pregnancy outcomes:

Pregnancies were classified according to pregestational BMI: 479 pregnancies (62.1%) were in class 1 (C1) defined by BMI < 25 kg/m² (including 15 pregnancies (2%), with a BMI < 18.5 kg/m²), 188 pregnancies (24.4%) in class 2 (C2) defined by BMI ≥ 25 and < 30 kg/m², and 104 pregnancies (13.5%) in class 3 (C3) defined by BMI ≥ 30 kg/m² *(Table 1).*

- *Comparison of baseline maternal characteristics according to BMI's classes:*

Supplementary Data 1 shows these data. Note the existence of some notable differences by pregestational BMI class. Class 3 (C3) had a lower proportion of smoking patients (14.3%) compared to the other two classes (class 1 (C1): 31.2% and class 2 (C2): 28.5%), and this was even more so during pregnancy. The median duration of diabetes was longer in C3: 16.5 years (IQR, 11 to 21) versus 14 years (IQR, 7 to 20) for C1. Furthermore, ¾ of obese patients were treated with CSII, compared with just over half of patients with a "normal" BMI. Finally, we found a higher proportion of hypertension in pre-pregnancy obese patients (8.8% versus

about 3% in the other two classes), whereas they had slightly less diabetic retinopathy. C1 is distinguished by a twice as high proportion of HbA1c <6.5% (47.5 mmol/mol), with a slightly lower median HbA1c before pregnancy. Diabetic nephropathy was almost twice as high in overweight patients compared with patients with a "normal" BMI. There was no difference for age at onset of pregnancy, nulliparity, or patients without any complications.

- *Comparison of adverse maternal outcomes according to BMI's classes:*

Supplementary Data 2 shows these data. The mean gestational HbA1c was lower in C1 compared with C2 (6.51 ± 0.79% (47.7 ± 5.8 mmol/mol) and 6.72 ± 0.73% (49.9 ± 5.4 mmol/mol), respectively). More cases of development or progression of retinopathy, nephropathy and, as expected, gestational hypertension and preeclampsia were found in C3. There was a modest increase in the proportion of postpartum hemorrhage with increasing pregestational BMI: from 7.8% in C1 to 12% in C3. Twice as many cases of ketoacidosis in normo-weighted patients were reported, with no clear difference in ICU transfers. Concerning the maternal composite criterion, there was a higher percentage of obese women (C3) presenting at least one of the elements composing this composite criterion (61.5% versus approximately 50% for the other classes).

- *Comparison of fetal characteristics and outcomes according to BMI's classes:*

Supplementary Data 3 shows these data. There was no difference concerning terms, but we described a higher frequency of prematurity in obese patients (C3) (26% versus about 20% in the other classes). The birth weight was higher with a greater proportion of LGA and macrosomia in C2. However, the occurrence of shoulder dystocia was slightly more frequent in normo-weighted women (C1). There was no difference in the proportions of SGA and neonatal malformations according to pregestational BMI. An Apgar score < 7 at 1 minute of life was more frequently found in overweight (C2) or obese (C3) women, while arterial pH was more frequently < 7.15 in obese women only (C3). We noted a more frequent occurrence of neonatal respiratory distress in C3, with no difference regarding neonatal ICU transfers. A higher proportion of IUFD was noted in C3 patients (3.7% vs. 0.5%). No difference was noted for the fetal composite criterion.

- *Pregestational BMI according to BMI's classes and pregnancy outcomes:*

Table 3 presents the results regarding the impact of pregestational BMI on adverse maternal or fetal outcomes assessed by our composite criteria. Adjustments were made for mean HbA1c during pregnancy, year of delivery, and type of treatment (insulin versus CSII). C1 was chosen as the reference. For the maternal composite criterion, no significant difference was found between the three BMI classes before and after adjustment. The closest OR to significance was for class 3 before adjustment: OR=1.52 (CI 95%=0.93 to 2.48; p=0.096); the trend disappeared after adjustment. For the fetal composite criterion, there was no significant difference between the three BMI classes before and after adjustment. The OR closest to significance was for class 2 before adjustment: OR=1.33 (CI 95%=0.9 to 1.94; p=0.15); the trend also disappeared after adjustment. The LGA was studied: no statistically significant difference between the three BMI classes was found. C2 seems to tend towards significance before adjustment (OR=1.37 (CI 95%=0.97 to 1.94; p=0.072)). However, the effect disappeared after adjustment. Concerning preeclampsia criterion: no significant association between the three BMI classes, with the OR closest to significance for C3 OR=1.53 (CI 95%=0.84 to 2.81; p=0.17), the trend decreased after adjustment. Finally, the prematurity criterion did not show any significant difference according to weight class (p>0.20).

4) DISCUSSION:

The aim of this study was to show to what extent pregestational BMI influences the occurrence of maternal or/and fetal adverse pregnancy outcome during type 1 diabetes pregnancies. A wide range of complications was studied. However, in this longitudinal cohort monocentric study, Odds Ratio (OR) for the proposed composite criteria (maternal or fetal), for LGA, for prematurity and for preeclampsia criteria did not find a significant increase in risks, suggesting that pregestational BMI is not an independent risk factor for the occurrence of maternal-fetal complications in pregnancies of women with type 1 diabetes.

Regarding baseline maternal characteristics, the proportions of overweight or obese women, mean age, duration of diabetes, percentage of CSII *versus* multi-daily injections and proportion of pre-pregnancy microangiopathic complications in our cohort of 764 pregnancies of type 1 diabetic patients were similar to other published cohort available on literature (36–39). However, our cohort was distinguished by a higher proportion of smokers: 28.3%, compared with 5 to 20% in various international studies (31,39–42). Habits vary according to regions and countries and finally, this proportion of women smokers is similar to that described in a recent epidemiological study representative of the French population in 2020 (43). Despite this criterion, our population could be considered as representative of the background population.

Many risk factors are associated with an unfavorable pregnancy outcome: parity, history of macrosomia, multiple pregnancy … (44). In the case of type 1 diabetes during pregnancy, we have shown in a previous study that metabolic imbalance was not sufficiency to explain maternal and fetal morbidity (25). For about 20 years, the management of obesity during pregnancy has been a source of interest. Indeed, different studies have shown an association between obesity and maternal-fetal complications with, in the first place, a significant risk of LGA and shoulder dystocia. These pregnancy complications in overweight women have a complex pathophysiology. A chronic pro-inflammatory state, linked to adipocyte dysfunction (especially a decrease in circulating levels of certain adiponectin isoforms), associated with disorders of lipid metabolism, mainly leading to a decrease in insulin sensitivity (14) and multifactorial placental dysfunction (15) seem to be the main suspected mechanisms in non-diabetic obese women (13). Recommendations to evaluate pregestational BMI have been proposed by the WHO: BMI ≤ 18.5 kg/m^2 (“underweight”), BMI ≥ 18.5 kg/m^2 and < 25 kg/m^2 ("normo-weighted"), BMI ≥ 25 kg/m^2 and < 30 kg/m^2 ("overweight"), and BMI ≥ 30 kg/m^2 ("obese") (8). Note that we decided to associate patients with low BMI (i.e., BMI < 18.5 kg/m^2) and the "normo-weighted" class because of the insufficient number of patients with low BMI in our cohort.

After classification according to pregestational BMI, some particularities appeared. The percentage of patients who were overweight or obese is superposable to other large Northern European (36,40,41,45,46) and American studies (7). The category of obese patients is characterized by half the proportion of smokers before pregnancy compared to other weight classes, with only 1 obese patient continuing to smoke actively during her pregnancy. This could be attributed to a possible greater attention of doctors to cardiovascular risk factors in these obese patients, and we could also evoke the potential weight gain secondary to the cessation of smoking, which is however moderate in most cases (47,48). Overweight women (BMI > 25 kg/m^2) are more often treated with CSII, while having a higher pregestational HbA1c, and especially less than half as many women had a pregestational HbA1c < 6.5% (47.5 mmol/mol), which is the recommend HbA1c at conception according to French (33) and American recommendations (34). Indeed, The American Diabetes Association suggests an HbA1c ≤ 6.5% (47.5 mmol/mol) before pregnancy or < 6% (42.1 mmol/mol) in the absence of hypoglycemia in this particular category of diabetes preexisting before pregnancy (34). In addition, obtaining an HbA1c < 6.5% (47.5 mmol/mol) in type 1 diabetics in preconception is sometimes difficult, which is why a target < 7% (53 mmol/mol) in preconception is regularly tolerated. In this cohort, 40.8 % of women had an HbA1c ≤ 7% (53 mmol/mol) in early pregnancy, allowing us to qualify this point. Besides, lot of articles over the last decade have largely confirmed the impact of a good metabolic control before pregnancy on maternal-fetal

morbidity reason why we adjusted our result on glycemic balance. The difficulty of balancing diabetes in these overweight women, is linked to increased insulin resistance secondary to the metabolic effects of excess altered adipose tissue, which is well demonstrated in the mouse model (49). Probably, this is one of the reasons that may explain the greater number of insulin pumps in this group (50). Our results were therefore calculated for the composite criteria, LGA, prematurity and preeclampsia without and with adjustment for year of delivery, mean HbA1c during pregnancy, and insulin therapy mode considering these remarks.

Concerning the presence of vascular complications, an impact of excess weight on the higher presence of diabetic nephropathy and hypertension at baseline may be suspected (51). As found in most published studies, our results seems to show that overweight and especially obese T1D patients have an increased risk of developing or worsening proteinuria and gravidic hypertension that can lead to preeclampsia (36,45). Regarding preeclampsia: our results suggest an increased risk in case of high BMI, i.e. > 30 kg/m^2. It is interesting to note that the literature shows some discordant results. Indeed, an American cohort from the end of the 20th century did not show a statistically significant association between type 1 diabetics with a BMI > 25 kg/m^2 and preeclampsia (52) where there is a small number of obese patients, as can be reproached to other more recent cohorts (32,53). On the contrary, Persson et al. showed in 2012, in their large cohort from national registries including 3457 type 1 diabetics, a significant association, with an OR=1.74 [95% CI 1.35; 2.25] in obese type 1 diabetics, in comparison with normo-weighted patients but without adjustment for glycemic and blood pressure control (36). Recently, the link between obesity and preeclampsia in type 1 diabetics were confirmed by the analysis of Persson et al. in 2016 with 7062 T1D women (45), and by a meta-analysis of 11,518 pregnancies among 11 articles (prevalence of preeclampsia 17% *vs.* 12% of all pregnancies in our cohort), with a significant influence of pregestational BMI in 8 of the 11 articles (54). Adipose tissue dysregulations contributed on the occurrence of preeclampsia are poorly known, or the results of analyzes are contradictory: Hendler et al. showed that in women with preeclampsia, those with a BMI ≥ 25 kg/m^2 had lowered adiponectin levels, whereas normo-weighted women had higher levels (55); contrary to the conclusions of Mazaki-Tovi et al, who did not find such a decrease in adiponectin levels, but rather a decrease in a ratio reflecting adiponectin activity, thus suggesting an altered regulation of this adipokine in preeclampsia (56). Studies on diabetic retinopathy in pregnancy have mainly focused on the influence of glycemic control, the duration of diabetes and the presence of micro or macroangiopathic complications prior to pregnancy, whereas being overweight is not considered a direct risk factor for the onset or progression of retinopathy (57–59). Our analysis shows a slightly higher proportion in obese people. It seems legitimate to consider overweight

as an indirect risk factor in the unfavorable evolution of retinopathy, given its possible responsibility in poor glycemic and blood pressure control.

Concerning obstetrical complications, a French study published in 2021, including 9159 non-diabetics patients between 2002 and 2018, showed a linear significant excess risk of emergency caesarean section in overweight/obese women (OR=1.78 [95% CI 1.52; 2.10] and OR=3.39 [95% CI 2.04; 5.63] in class 3 obesity, i.e. BMI ≥ 40 kg/m^2) (60), identically as an American study in 2010 after an adjustment on metabolic balance (61). Similarly, the increased risk of scheduled or emergency caesarean section is well described in a Swedish study (36) where the analysis of 3457 type 1 diabetes pregnancies from 1997 to 2007, shows an OR=1.37 [95% CI 1.18; 1.60] and 1.67 [95% CI 1.38; 2.03] respectively in overweight and obese women in comparison with normo-weighted type 1 diabetics women. No adjustment for glycemic control and excluding extreme weights (>200kg) were made in this analysis. Note that several studies did not show a statistically significant association between high pregestational BMI and caesarean section: possibly populations were too small? (37,62). Frequent situations leads to cesarean section in obese patients: preeclampsia (45), macrosomia (36,62), poor uterine contractility (63) leading to ineffective labour, or non-reassuring fetal status (64). Unfortunately, no information was available to specify indications for caesarean sections. Our study suggests a slightly lower occurrence of vaginal mode of delivery in obese women, which it be biased by a possible greater use of caesarean section in these women considered at high-risk.

Concerning the main fetal complications, prematurity and excessive fetal growth (LGA and macrosomia) are predominant. The occurrence of prematurity, was found in 33% to 44% of pregnancies of type 1 diabetics (42,62,65) (except for Persson and al., published in 2012: prematurity rate was 21% (36)), whereas it was only 21.5% in our study. Equally, a lower rate of preeclampsia (45,54,65) was found in our cohort. Perhaps, the regular and rigorous follow-up in our tertiary care center, could lead to a decrease in these occurrences (center effect).

The proportion of LGA in type 1 diabetes ranges from 49-52% of pregnancies in literature, which corresponds to the proportion found in our study (36,66). According to Persson et al., there is a very small statistically significant effect of increased pregestational BMI on the occurrence of LGA (OR=1.18 [95% CI 1.01; 1.38] and OR=1.21 [95% CI 1; 1.47] respectively for overweight and obese women), with a small increase in the risk of macrosomia in obese T1D women, with an OR=1.36 [95% CI 1.09; 1.69], normo-weighted T1D women as reference (36). In our cohort, overweight women had a higher proportion of LGA and macrosomia, with logically a significantly higher birth weight, which may be related to their poorer glycemic control, with a higher mean HbA1c than other weight classes. Nevertheless, we failed to show

a statistically significant relationship between the occurrence of LGA and weight classes in our cohort. The difference in HbA1c between overweight and obese women may be explained by a follow-up bias, with a possible reinforcement of glycemic monitoring in obese patients. Numerous definitions and criteria exists concerning neonatal malformations (early death or major functional deficit such as cardiac, nervous system or digestive malformations *versus* functional and aesthetic disabilities such as cleft palate or skeletal abnormalities) (36,62,66–69). Thus, the prevalence varying from 4% to 9% in type 1 diabetics in accordance with our results. There are few data in the literature regarding shoulder dystocia, pH, Apgar score, respiratory distress and transfer to neonatal ICU in newborns of mothers with T1D. In 2017, Sven Cnattingius et al. showed in a study comparing 5941 newborns of type 1 diabetic women with more than 1.3 million newborns of non-diabetic women, that there is a significant increase in the risk of occurrence of an Apgar score < 7 at 5 minutes of life in newborns of type 1 diabetic mothers with increasing pregestational BMI, but with no significant difference with non-diabetic women (40). A Chinese study from 2020 shows a significant increase in the risk of transfer to neonatal intensive care in case of HbA1c ≥ 6% (42.1 mmol/mol) at delivery, but without adjustment for pregestational weight (65). We systematically transfer risky premature newborns, or from emergency caesarean sections in our center. Certain that different protocols exist elsewhere.

We decided to evaluate morbidity and mortality assessed by a maternal and fetal composite criteria, as a previous study carried out in our center, looking at the impact of HbA1c, proposed a composite criterion made up of the most common complications (LGA, SGA, preeclampsia, caesarean section and prematurity) (25). In this study, we have decided to propose a maternal composite criterion and a fetal composite criterion, made up of the complications that we consider to be the most relevant. The impact of pregestational BMI on the most frequent complications has also been assessed in isolation. To limit bias, association studies were adjusted for year of delivery, mean HbA1c during pregnancy, and treatment modality. No significant association for the proposed composite criteria and for the LGA, prematurity and preeclampsia criteria was find, suggesting that pregestational BMI was not an independent risk factor for the occurrence of maternal-fetal complications in pregnancies of women with type 1 diabetes. However, there appears to be a trend. Our composite criteria were present in 54% for maternal complications and 69% for fetal complications, suggesting a good sensitivity. All the elements selected are clinically relevant for specialists caring for pregnant patients with type 1 diabetes. Our choice has been made for adverse outcomes (retinopathy, proteinuria, caesarean section, prematurity) whose proportion was probably not sufficiently discriminating between the different weight classes. Rarer adverse outcomes (postpartum hemorrhage,

shoulder dystocia, SGA, congenital malformations, respiratory distress) were also examined; however, there was an identical distribution between the weight classes.

Several strengths characterize this study: this is the largest cohort of type 1 diabetic pregnant patients who have been followed in the same center by a medical and paramedical team trained in the problems of diabetic pregnant women, allowing comparable diabetic and obstetrical management on the 24 years of study, and concern a wide range of maternal and neonatal complications. Unfortunately, some biases and weaknesses must be noted: retrospective design including sometimes a lack of data, particularly concerning the glycemic control, and no information concerning ethnic origin, and neonatal hypoglycemia. Missing data could nevertheless be compensated by multiple imputations, that could generate a lack of power in the statistical comparisons. Moreover, data concerning the use of continuous glucose monitoring are not available, although the benefit of its use on the occurrence of neonatal complications was demonstrated by a first randomized controlled study published in 2017, in type 1 diabetic patients (39). The Jeanne de Flandres Hospital is a tertiary care center, which takes care of the most high-risk pregnancies, with a very wide recruitment within the Northern region of France. Thus, there is a "center effect" which probably overestimates the frequency of occurrence of maternal-fetal complications. Finally, as the number of women with a low BMI was insufficiency (15 individuals) compared to the other weight categories, this would not have allowed us to perform adequate analyses in this weight class.

In conclusion, our results suggest a more frequent occurrence of most maternal and fetal complications in pregnancies of women with type 1 diabetes, without association with pregestational BMI. However, in view of the frequency of maternal-fetal complications, it seems important to understand and optimize pregestational weight at the same time as metabolic control. Specific and individualized management of diabetic and obese pregnant women, with particular attention to weight gain during pregnancy, seems essential.

5) TABLES & FIGURES:

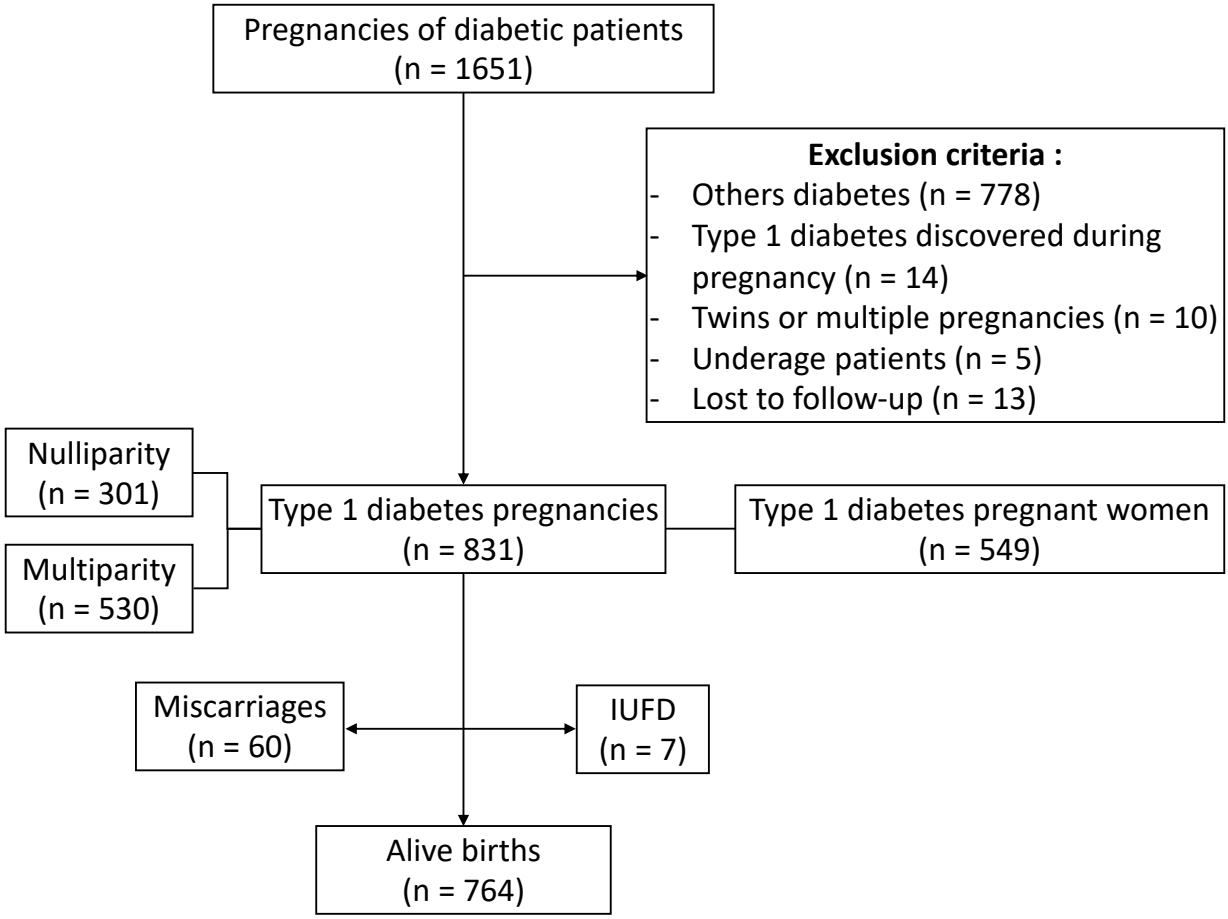


Figure 1 : Patients enrollment flow-chart

Table 1: Baseline maternal characteristics

Maternal characteristics*	**N**	**Values**
Age, years	771	29.4 ± 4.9
Height, m	771	1.65 ± 0.06 [d]
Weight before pregnancy, kg	771	67.41 ± 13.78 [d]
BMI before pregnancy, kg/m²	755	24.85 ± 4.82
Normo-weighted before pregnancy	771	479 (62.1) [d]
Overweighted before pregnancy	771	188 (24.4) [d]
Obese before pregnancy	771	104 (13.5) [d]
Smoking before pregnancy	604	171 (28.3)
Smoking during pregnancy	580	95 (16.4)
Duration of diabetes, years	769	14 (8 ; 20)
Continuous subcutaneous insulin infusion	771	456 (59.1)
FIT before pregnancy	771	228 (29.6)
HbA1c before pregnancy, %, mmol/mol	690	7.15 (6.6 ; 8), 54.6 (48.6 ; 63.9)
HbA1c below 6.5% before pregnancy	690	126 (18.3)
No complication	768	541 (70.4)
Diabetic retinopathy	771	200 (25.9)
Diabetic nephropathy	771	54 (7)
Hypertension	771	30 (3.9)
Nulliparity	771	279 (36.2)
Values are expressed as number (%), or mean ± SD, or median (IQR)		
SD: standard deviation, IQR: interquartile range		
BMI: body mass index		
FIT: functional insulin therapy		
IUFD: intrauterine fetal death * : including IUFD [d] : after multiple imputation		

Table 2: Maternal and fetal characteristics and outcomes, all weights combined

	N	Values	After multiple imputation (N = 771)*
Maternal outcomes			
1st trimester HbA1c, %, mmol/mol	689	6.87 ± 1.07, 51.6 ± 8	6.91 ± 1.09, 52 ± 8.2
2nd trimester HbA1c, %, mmol/mol	715	6.42 ± 0.80, 46.7 ± 5.8	6.42 ± 0.80, 46.7 ± 5.8
3rd trimester HbA1c, %, mmol/mol	650	6.50 ± 0.81, 47.5 ± 5.9	6.54 ± 0.85, 48 ± 6.2
HbA1c during pregnancy, %, mmol/mol	715	6.47 (6.03 ; 6.97), 47.2 (42.4 ; 52.7)	
Diabetic retinopathy evolved	736	195 (26.5)	206 (26.7)
Proteinuria evolved	765	181 (23.7)	184 (23.8)
Gravidic hypertension	765	129 (16.9)	131 (17.0)
Preeclampsia	765	90 (11.8)	92 (11.9)
Vaginal delivery	766	389 (50.8)	
Labor induction before successful vaginal delivery	389	285 (73.3)	
Operative vaginal delivery	389 [a]	163 (41.9) [a]	
	766 [c]	163 (21.2) [c]	
Cesarean section	766	377 (49.2)	
Emergency cesarean section before labour	366 [b]	84 (23) [b]	
	764 [c]	84 (11) [c]	
Postpartum hemorrhage	682	59 (8.7)	85 (11.0)
Ketoacidosis during pregnancy	771	24 (3.1)	24 (3.1)
Intensive Care Unit admission	771	9 (1.2)	
Maternal composite criterion	711	386 (54.3)	404 (52.3)
Fetal outcomes			
Term, weeks	769	38 (37 ; 38.4)	
Prematurity	769	164 (21.3)	166 (21.5)
Male	767	392 (51.1)	
Birth weight, grams	758	3507 ± 678	
Macrosomia	758	173 (22.8)	
LGA	758	402 (53.0)	405 (52.5)
SGA	758	14 (1.9)	23 (3.0)
Severe neonatal malformations	763	59 (7.7)	61 (7.9)
Shoulder dystocia	742	59 (8.0)	66 (8.5)
Apgar score < 7 at 1 min.	697	68 (9.8)	
Apgar score < 7 at 5 min.	697	19 (2.7)	
Arterial pH < 7.15	533	133 (24.5)	
Arterial pH < 7	533	13 (2.4)	
Respiratory distress	740	70 (9.5)	74 (9.6)
Neonatal Intensive Care Unit Admission	751	104 (13.8)	110 (14.3)
IUFD	771	7 (0.9)	7 (0.9)
Fetal composite criterion	759	524 (69.0)	529 (68.6)

Values are expressed as number (%), mean ± SD, median (IQR)
SD: standard deviation, IQR: interquartile range
LGA: large for gestational age
SGA: small for gestational age
IUFD: intrauterine fetal death

Maternal composite criterion: at least 1 complication among diabetic retinopathy, proteinuria, gravidic hypertension, preeclampsia, postpartum hemorrhage or ketoacidosis
Fetal composite criterion: at least 1 complication among prematurity, LGA, SGA, shoulder dystocia, severe malformations, respiratory distress or intensive care unit admission
These criteria are positive if at least one of the elements is present

* : including intrauterine fetal deaths
[a] : vaginal deliveries only
[b] : cesarean sections only
[c] : all deliveries included

Table 3: Pregestational BMI according to BMI classes and pregnancy outcomes

	Complications		Unadjusted		Adjusted	
	No	**Yes**	**Odds Ratio (95%CI)**	**p**	**Odds Ratio (95%CI)**	**p**
Maternal CC	N = 368	N = 403				
BMI classes				0.18		0.35
1	234 (63.55)	245 (60.82)	1.00 (ref.)	-	1.00 (ref.)	-
2	94 (25.56)	94 (23.35)	0.95 (0.65 to 1.39)	0.81	0.90 (0.61 to 1.34)	0.63
3	40 (10.89)	64 (15.82)	1.52 (0.93 to 2.48)	0.096	1.34 (0.83 to 2.17)	0.24
Mean ± SD	24.57 ± 4.70	25.11 ± 4.93	1.02 (0.99 to 1.06)	0.18	1.01 (0.98 to 1.05)	0.47
Fetal CC	N = 242	N = 529				
BMI classes				0.36		0.61
1	158 (65.18)	321 (60.75)	1.00 (ref.)	-	1.00 (ref.)	-
2	51 (21.04)	137 (25.94)	1.33 (0.90 to 1.94)	0.15	1.23 (0.82 to 1.84)	0.32
3	33 (13.78)	71 (13.32)	1.03 (0.66 to 1.64)	0.88	0.98 (0.60 to 1.62)	0.94
Mean ± SD	24.56 ± 4.91	24.99 ± 4.78	1.02 (0.99 to 1.05)	0.26	1.01 (0.98 to 1.05)	0.45
Preeclampsia	N = 679	N = 92				
BMI classes				0.37		0.68
1	425 (62.63)	54 (58.52)	1.00 (ref.)	-	1.00 (ref.)	-
2	167 (24.57)	21 (23.13)	1.01 (0.58 to 1.74)	0.98	0.96 (0.55 to 1.68)	0.89
3	87 (12.80)	17 (18.35)	1.53 (0.84 to 2.81)	0.17	1.29 (0.69 to 2.42)	0.42
Mean ± SD	24.80 ± 4.84	25.24 ± 4.68	1.02 (0.97 to 1.06)	0.42	1.01 (0.96 to 1.05)	0.77
LGA	N = 366	N = 405				
BMI classes				0.17		0.35
1	237 (64.61)	243 (59.91)	1.00 (ref.)	-	1.00 (ref.)	-
2	78 (21.35)	110 (27.15)	1.37 (0.97 to 1.94)	0.072	1.27 (0.89 to 1.83)	0.19
3	51 (14.05)	52 (12.93)	0.99 (0.64 to 1.55)	0.98	0.94 (0.59 to 1.50)	0.79
Mean ± SD	24.74 ± 5.04	24.96 ± 4.62	1.01 (0.98 to 1.04)	0.54	1.00 (0.97 to 1.04)	0.85
Prematurity	N = 606	N = 165				
BMI classes				0.34		0.33
1	378 (62.44)	101 (61.03)	1.00 (ref.)	-	1.00 (ref.)	-
2	152 (25.04)	37 (22.05)	0.90 (0.58 to 1.39)	0.64	0.88 (0.56 to 1.39)	0.58
3	76 (12.52)	28 (16.92)	1.38 (0.84 to 2.29)	0.21	1.41 (0.83 to 2.42)	0.21
Mean ± SD	24.69 ± 4.67	25.43 ± 5.30	1.03 (0.99 to 1.07)	0.094	1.03 (0.99 to 1.07)	0.086

Values are expressed as number (%), mean ± SD
SD: standard deviation
CI: confidence interval
LGA: large for gestational age
CC: composite criterion
CSII: continuous subcutaneous insulin infusion
BMI: body mass index

BMI class 1: BMI < 25 kg/m², class 2: BMI ≥ 25 and < 30 kg/m², class 3: BMI ≥ 30 kg/m²

Maternal composite criterion: at least 1 complication among diabetic retinopathy, proteinuria, gravidic hypertension, preeclampsia, postpartum hemorrhage or ketoacidosis
Fetal composite criterion: at least 1 complication among prematurity, LGA, SGA, shoulder dystocia, severe malformations, respiratory distress or intensive care unit admission
These criteria are positive if at least one of the elements is present
Adjustments were made for mean HbA1c during pregnancy, year of delivery and type of treatment (insulin versus CSII)

Supplementary Data 1: Maternal pregestational characteristics according to BMI classes

Pre-pregnancy characteristics :	**BMI classes**		
	Class 1	Class 2	Class 3
Age, years	29.33 ± 4.76	29.46 ± 5.21	29.88 ± 5.17
Smoking before pregnancy	31.2 (114/365)	28.5 (43/151)	14.3 (12/84)
Smoking during pregnancy	20.7 (73/352)	14.1 (20/142)	1.2 (1/82)
Duration of diabetes, years	14 (7 ; 20)	15 (9 ; 20)	16,5 (11 ; 21)
CSII	55.3 (259/468)	63 (116/184)	73.5 (75/102)
HbA1c before pregnancy, %, mmol/mol	7.1 (6.5 ; 8), 54.1 (47.5 ; 63.9)	7.3 (6.8 ; 8.2), 56.3 (50.8 ; 66.1)	7.2 (6.8 ; 8.1), 55.2 (50.8 ; 65)
HbA1c below 6,5 % before pregnancy	22.5 (95/423)	11.3 (19/168)	12.1(11/91)
No complication	71.4 (334/468)	66.3 (122/184)	72.5 (74/102)
Diabetic retinopathy	26.5 (124/468)	28.3 (52/184)	19.6 (20/102)
Diabetic nephropathy	5.6 (26/468)	10.3 (19/184)	6.9 (7/102)
Hypertension	3.4 (16/468)	2.7 (5/184)	8.8 (9/102)
Nulliparity	38.2 (179/468)	31.5 (58/184)	34.3 (35/102)

Values are expressed as % (number/total), or mean ± SD, or median (IQR)

SD: standard deviation, IQR: interquartile range

CSII: continuous subcutaneous insulin infusion

BMI: body mass index

Class 1: BMI < 25 kg/m², class 2: BMI ≥ 25 and < 30 kg/m², class 3: BMI ≥ 30 kg/m²

Supplementary Data 2: Maternal outcomes according to BMI classes

Adverse maternal outcomes :	**BMI classes**		
	Class 1	Class 2	Class 3
HbA1c during pregnancy, %, mmol/mol	6.51 ± 0.79, 47.7 ± 5.8	6.72 ± 0.73, 49.9 ± 5.4	6.57 ± 0.69, 48.3 ± 5.1
Diabetic retinopathy evolved	25.9 (116/448)	26 (46/177)	32.3 (31/96)
Gravidic hypertension	15.6 (73/467)	14.8 (27/182)	25 (25/100)
Proteinuria evolved	22.7 (106/467)	24.2 (44/182)	26 (26/100)
Preeclampsia	10.9 (51/467)	11 (20/182)	16 (16/100)
Cesarean section	43.7 (204/467)	56.8 (104/183)	60.6 (60/99)
Cesarean section due to cervical dystocia [b]	25.1 (50/199)	20.4 (21/103)	15.8 (9/57)
Emergency cesarean section before labour	19.3 (39/202) [b] 8.4 (39/466) [c]	25 (26/104) [b] 14.2 (26/183) [c]	26.7 (16/60) [b] 16.3 (16/98) [c]
Operative vaginal delivery	43.3 (114/263) [a] 24.4 (114/467) [c]	46.8 (36/77) [a] 19.9 (36/181) [c]	32.4 (12/37) [a] 12.4 (12/97) [c]
Postpartum hemorrhage	7.8 (32/408)	9.6 (16/166)	12 (11/92)
Ketoacidosis during pregnancy	3.6 (17/468)	1.)6 (3/184)	2 (2/102)
Intensive Care Unit admission	1.1 (5/468)	1.6 (3/184)	0/102
Maternal composite criterion [d]	51.1 (245/479)	50 (94/188)	61.5 (64/104)

Values are expressed as % (number/total), or mean ± SD, or median (IQR)

SD: standard deviation, IQR: interquartile range
BMI: body mass index
Class 1: BMI < 25 kg/m², class 2: BMI ≥ 25 and < 30 kg/m², class 3: BMI ≥ 30 kg/m²

Maternal composite criterion: at least 1 complication among diabetic retinopathy, proteinuria, gravidic hypertension, preeclampsia, postpartum hemorrhage or ketoacidosis

This criterion is positive if at least one of the elements is present

[a] : vaginal deliveries only
[b] : cesarean sections only
[c] : all deliveries included
[d] : after multiple imputation

Supplementary Data 3: Fetal characteristics and outcomes according to BMI classes

Fetal characteristics and outcomes :	BMI classes		
	Class 1	Class 2	Class 3
Delivery terms, amenorrhea weeks	38 (37 to 38.4)	38 (37.1 to 38.3)	38 (36.9 to 38.4)
Prematurity	20.7 (97/468)	19 (35/184)	26 (26/100)
Birth weight, grams	3476 ± 665	3626 ± 683	3482 ± 643
Macrosomia	21 (97/463)	28.3 (51/180)	22.4 (22/98)
LGA	51.2 (237/463)	59.4 (107/180)	51 (50/98)
SGA	1.9 (9/462)	1.7 (3/180)	2 (2/98)
Severe neonatal malformations	7.7 (36/465)	6.6 (12/183)	8.2 (8/98)
Shoulder dystocia	9.2 (42/456)	5.6 (10/178)	7.7 (7/91)
Apgar score < 7 at 1 min.	7.7 (33/426)	12.5 (21/168)	12.6 (11/87)
Apgar score < 7 at 5 min.	2.6 (11/426)	2.4 (4/168)	3.4 (3/87)
Arterial pH < 7.15	22.3 (70/314)	20.5 (27/132)	38.4 (28/73)
Arterial pH < 7	3.2 (10/314)	0/132	2.7 (2/73)
Respiratory distress	9.2 (42/455)	8.4 (15/178)	12.2 (11/90)
Neonatal Intensive Care Unit admission	13.5 (62/459)	14.9 (27/181)	12.8 (12/94)
IUFD	0.4 (2/504)	0.5 (1/200)	3.7 (4/102)
Overall fetal composite criterion [d]	67 (321/479)	72.9 (137/188)	68.3 (71/104)

Values are expressed as % (number/total), or mean ± SD, or median (IQR)

SD: standard deviation, IQR: interquartile range
LGA: large for gestational age
SGA: small for gestational age
IUFD: intrauterine fetal death
BMI: body mass index
Class 1: BMI < 25 kg/m², class 2: BMI ≥ 25 and < 30 kg/m², class 3: BMI ≥ 30 kg/m²

Fetal composite criterion: at least 1 complication among prematurity, LGA, SGA, shoulder dystocia, severe malformations, respiratory distress or intensive care unit admission
This criterion is positive if at least one of the elements is present

[d] : after multiple imputation

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Dans la littérature mais également dans une étude récente issue de notre centre, nous avons montré que les femmes diabétiques de type 1 conservent un risque supérieur de complications materno-fœtales malgré une correction de leur équilibre métabolique au cours de la grossesse.

D'après ce premier article, le surpoids et l'obésité pré-gestationnels, définis respectivement par un IMC ≥ 25 et < 30 kg/m^2 ou un IMC ≥ 30 kg/m^2 avant le début de la grossesse, n'apparaissent pas comme des facteurs de risque indépendants pour la survenue d'un large panel de complications, appréciées à l'aide de critères composites, au sein de notre cohorte.

Nous avons donc tenté d'expliquer cette persistance du risque par une analyse tenant compte à présent de la prise de poids gestationnelle. Les résultats issus de ce travail vous sont présentés dans l'article scientifique suivant :

IV. Second article

L'excès de prise de poids au cours des grossesses marquées par la présence d'un diabète de type 1 est-il associé à un excès de morbidité materno-fœtale ?

2nd article:

Is excess weight gain during pregnancy in women with type 1 diabetes mellitus associated with excess maternal-fetal morbidity?

1) INTRODUCTION:

Since the St. Vincent's declaration, the optimization of diabetes management in pregnancy has evolved with the goal of having the same morbidity between diabetic and non-diabetic women during pregnancy [1]. However, there is still persistent maternal and fetal morbidity, especially with regard to pregestational diabetes [2]. In our center, we have shown that first and third trimester metabolic imbalance is associated with greater morbidity in the type 1 pregestational diabetes population regarding LGA (Large for Gestational Age), SGA (Small for Gestational Age), prematurity, cesarean section, and preeclampsia assessed by a maternal-fetal composite criterion. Despite a correction of metabolic imbalance in early pregnancy, this was not sufficient to eliminate this risk, suggesting other complementary mechanisms of involvement [3]. The contribution of obesity and gestational weight gain to morbidity has been highlighted in several studies.

Since the end of the 20th century, numerous data are available to measure the consequences of GWG (Gestational Weight Gain) on maternal-fetal morbidity. The Institute of Medicine (IOM) has developed guidelines for GWG to target an ideal birthweight. However, we know that there has been, according to the IOM and National Research Council in 'Re-examining the Guidelines', an upward trend in GWG from 1990 to 2005 [4]. Strong associations have been described for cesarean section and medium-term postpartum weight retention for mothers, and for birth weight, LGA or SGA, prematurity for newborns [5]. In 2009, the IOM proposed new guidelines for weight gain during pregnancy to improve maternal and infant health by considering pregestational BMI: low BMI (<18.5 kg/m^2), normal BMI (≥18.5-<25.0 kg/m^2), high BMI (≥25.0- <30.0 kg/m^2), obesity (≥ 30.0 kg/m2). Respectively, each category should have a GWG corresponding to: 12.7-18 kilograms, 11.3-15.9 kilograms, 6.8-11.3 kilograms, 5.0-9.0 kilograms [6]. No optimal weight gain guidelines specifically for women with pregestational diabetes have been proposed. However, excess weight gain is known to aggravate insulin resistance and affect diabetes outcomes in non- pregnant individuals with type 1 diabetes [7].

Excess weight gain in non-diabetic women during pregnancy is marked by excess morbidity. Cosson & al., in 2016, studied the impact of excess gestational weight gain in glucose normotolerant women and showed a significant association with the risk of SGA (for weight gain <7.5 kilograms) and LGA: OR=1.64 [96% CI 1.38-1.95] for weight gain of 11.6 to 16

kilograms, and OR=3.58 [95% CI 2.91-4.40] for weight gain >16 kilograms [8]. The combination of effects specific to excess gestational weight gain and metabolic effects in type 1 diabetic pregnancies is therefore possibly associated with greater morbidity.

The aim of this study was to define whether weight gain could be an explanatory factor for maternal and fetal adverse events during pregnancy in women with type 1 diabetes followed at the same tertiary care center and by the same multidisciplinary professionals. To this end, we sought to define whether, an excessive weight gain or in contrary a GWG inferior to the recommendations during pregnancy was associated with adverse maternal and fetal events, assessed by composite maternal and fetal criteria.

2) RESEARCH DESIGN:

Using electronic data including routinely collected metabolic and obstetric data, we conducted a single-center observational study regarding adverse pregnancy outcomes in women with type 1 diabetes, at the University Hospital of Lille, France. The data were collected at the time of delivery of each woman who had given birth. According to French law, patients are informed that their care data may be used for research purposes, unless they object to such use. These data were analyzed anonymously, and our database was declared to the French Committee for Computerized Data (CNIL). In this observational cohort, we analyzed all women with pregestational diabetes who gave birth between 1997 and 2021. Only pregnancies with type 1 diabetes were included. Exclusion criteria were represented by an age < 18 years, another type of diabetes (type 2 diabetes, syndromic diabetes or secondary diabetes), the presence of diabetes discovered during pregnancy, no data or consent, lost to follow up or twins/multiple pregnancies because they have a higher risk of adverse outcome.

Data collections:

Data of interest were collected from the patient records concerning the demographic, maternal obstetric and neonatal data of the women included in the study. Data concerning the history of diabetes were also collected: duration of evolution, type of treatment (CSII versus subcutaneous injections), practice of functional insulin therapy, pre-conceptional metabolic balance or the presence of micro and/or macro vascular complications. Diabetic and obstetric follow-up was performed monthly, and patients were called twice a week by a specialized nurse to assess glycemic control and adjust treatment if necessary. Patients were treated with short-acting insulin analogue before meals and a long-acting insulin analogue injection or continuous subcutaneous insulin infusion (CSII). Parity and gravidity, date of pregnancy, history of macrosomia, hypertension, preeclampsia, miscarriage or in utero fetal death (IUFD) were also

collected. All patients performed self-monitoring of blood glucose with glycemic targets <95mg/dL (5.23 mmol/l) before meals and <120 mg/dL (6.6 mmol/l) after meals. Obstetrical and diabetic follow-up was in accordance with French recommendations (respectively Société Francophone du Diabète (SFD) [9] and American recommendations [10]).

Age, height and weight were recorded, and BMI was calculated (weight/(height*height) in kg/m^2). Concerning weight gain, the Institute of Medicine (IOM) proposed guidelines for weight gain during pregnancy considering pregestational BMI: low BMI (< 18.5 kg/m^2), normal BMI (≥ 18.5 and < 25 kg/m^2), overweight (≥ 25 and < 30 kg/m^2) and obesity (≥ 30 kg/m^2). Respectively, each category should have a GWG corresponding to: 12.7-18 kilograms, 11.3-15.9 kilograms, 6.8-11.3 kilograms, 5-9 kilograms [6] Systolic and diastolic blood pressure were measured; hypertension was defined as blood pressure > 140/90 mmHg or use of antihypertensive medication before pregnancy.

Concerning maternal outcomes, vascular complications were reported: apparition or aggravation of retinopathy diabetic and its characteristics, apparition or aggravation of proteinuria and apparition or aggravation of hypertension. Preeclampsia was defined by association of systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg and proteinuria ≥ 300 mg/24 hours after 20 amenorrhea weeks. Delivery modalities were described: vaginal (spontaneous vaginal delivery, labor induction, or operative vaginal delivery) or cesarean section and in these cases if they were programed or realized in urgency. Number of cervical dystocia were counted. Ketoacidosis cases were collected, and Intensive Care Unit admission were reported. Concerning maternal adverse pregnancies outcomes, a maternal composite criterion (CCm) was defined: at least 1 complication among diabetic retinopathy, proteinuria, gravidic hypertension, preeclampsia, postpartum hemorrhage or ketoacidosis.

Concerning fetal outcomes, birth weight helped to define macrosomia as birth weight ≥ 4000 grams, LGA (Large for Gestational Age) or SGA (Small for Gestational Age) according to AUDIPOG formula (respectively > 90^{th} centile and < 10^{th} centile, which included the term, sex and birth weight). Prematurity was defined as delivery before 37 amenorrhea weeks. The rate of malformations leading to death, emergency care or disability was determined. Shoulder dystocia were defined using obstetrical maneuvers other than the gentle pull of the head or the restorative maneuver to free the fetal shoulders. Arterial pH was pathological if he was lower to 7.15 on umbilical cord blood gas analysis. Neonatal Intensive Care Unit admissions have been listed. Miscarriages and IUFD were respectively defined by the loss of pregnancy before and after 22 amenorrhea weeks; 22 amenorrhea weeks correspond at fetal viability. We

defined a fetal composite criterion (CCf) (associating prematurity, LGA, SGA, shoulder dystocia, severe malformations, respiratory distress or intensive care unit admission) for estimate proportion of fetal morbidity in our population. The criterion was positive if at least one component was present.

Statistical analyses :

Statistical analyses were conducted using SAS software (SAS Institute 9.4, Cary, USA). Categorical variables were reported as numbers (percentage). Quantitative variables were described by means ± standard deviation, in case of Gaussian distribution, or otherwise by median (interquartile range (IQR)). Normality of numerical variables was checked graphically and tested using the Shapiro-Wilk test.

Three pregnancy outcomes were investigated: maternal composite criterion, LGA and fetal composite criterion. We assessed the association of weight gain (in kg) with pregnancy outcomes using logistic regression models before and after adjustment on predefined confounding factors (HbA1c, year of delivery, type of treatment). Comparisons between the three classes of weight gain were made using logistical regression models before and after adjustment on predefined confounding factors, using class GW 0 as reference. We examined the log-linearity assumption for continuous features using restricted cubic spline functions. All results were expressed in odds ratios (OR) and their 95% confidence intervals (CI). To avoid bias, multiple imputations using the multivariate imputation by chained equations methodology were applied to account for missing data. The results of each imputed dataset were pooled using Rubin's rules. Statistical testing was done at the 2-tailed level of 0.05.

3) RESULTS:

Patient enrollment of type 1 diabetes population:

After screening of all pregnancies, 1651 pregnancies of women with preexisting diabetes have been identified: 778 type 2 diabetes mellitus or others diabetes pregnancies, 14 with types 1 diabetes discovered during pregnancy. Initially, 861 pregnancies were excluded for above-mentioned reasons. Finally, 831 pregnancies concerning 549 type 1 diabetic women were studied, corresponding to 50.3 % of all diabetic women pregnancies, with 764 alive births (60 miscarriages and 7 IUFD). 301 women were nulliparous (*Figure 1).*

Baseline maternal characteristics:

Type 1 diabetes pregnant women had a mean age at 29.4 ± 4.9 years, a mean BMI before pregnancy at 24.85 ± 4.82 kg/m^2. 28.3% (171/604) smoked before pregnancy and 16.4% did not quit smoking during pregnancy. Median duration of diabetes was 14 years (8; 20), and 59.1% (456/771) utilized a CSII, with a daily practice of functional insulin therapy for 29.6% (228/771). Median HbA1c before pregnancy was 7.15% (54.6 mmol/mol) (6.6; 8); only 18.3 % (126/690) obtained an HbA1c below 6.5% (47.5 mmol/mol) before pregnancy. Around 30% of pregnant women had vascular complication, comprising diabetic retinopathy (25.9 % (200/771)), diabetic nephropathy (7 % (54/771)), hypertension (3.9 % (30/771)) (*Table 1).*

Maternal and fetal adverse pregnancy outcome:

Results are presented after imputation. Median HbA1c during pregnancy was 6.47% (47.2 mmol/mol) (IQR, 6.03 to 6.97). Concerning vascular complications, diabetic retinopathy evolved in 26.7% of cases (206/771), gravidic hypertension in 17 % (131/771), apparition or aggravation of proteinuria was noted for 23.8 % (184/771) and preeclampsia concerned 11.9 % (92/771). During delivery, 50.8 % (389/766) were vaginal delivery and 49.2 % (377/766) cesarean section. 11 % (85/771) of women were concerned by postpartum hemorrhage. Ketoacidosis concerned 3.1 % (24/771) and 1.2 % (9/771) were admitted in ICU. The maternal composite criterion was found in 52.3% (404/771) of pregnancies, i.e., slightly more than ½ type 1 diabetic women had excess morbidity assessed by our maternal composite criterion.

Regarding adverse fetal outcomes, the gestational age at delivery was 38 (IQR, 37 to 38.4) weeks. The rate of prematurity was 21.5 % (166/771). Mean birth weight was 3507 ± 678 grams. The rate of macrosomia was 22.8 % (173/758), LGA was 52.5 % (405/771). The rate of SGA was 3 % (23/771). Shoulder dystocia concerned 8.6 % newborn. 7.9 % (61/771) of the children had a neonatal malformation. 14.3 % (110/771) needed Neonatal Intensive Care Unit admission. 24.5 % of children had an arterial pH < 7.15 translating a metabolism acidosis, and 2.4 % (13/533) had an arterial pH < 7. Apgar score < 7 at 1 min. and at 5 min. were respectively 9.8 % (68/697) and 2.7 % (19/697) of cases. Respiratory distress concerned 9.6 % of newborns (74/771). The CCf was present in 68.6 % (529/771) of cases, i.e., slightly more than 2 in 3 newborns of type 1 diabetic women had an excessive morbidity assessed by our fetal composite criterion (*Table 2*).

Weight gain and maternal-fetal adverse pregnancy outcome*:*

Pregnancies were classified according to weight gain: 129 pregnancies (18.3%) were classified as WG -1 (weight gain below the consensus goals), 219 pregnancies (31.1%) were classified as WG 0 (weight gain corresponding to consensual recommendations), and 350 pregnancies (49.6%) were classified as WG+1 (excessive weight gain in comparison to consensual recommendations). *Supplementary data 1* shows characteristics and adverse maternal/fetal outcomes concerning each category for each BMI's classes. *Table 4* presents the impact of weight gain on adverse maternal or fetal pregnancy outcomes assessed by our composite criteria. Adjustments were made for mean HbA1c during pregnancy, year of delivery, and type of treatment (insulin *versus* CSII). WG 0 was chosen as the reference, because this class was in adequation with the consensual recommendations. For the CCm, a significant difference was found between reference and WG +1 classes before adjustment: OR=1.44 [95% CI = 1.03 to 2.01; p=0.033]. However, we noted a disappearance of statistical significance after adjustment: OR=1.40 [95% CI 0.98 to 2.01; p=0.06]. For the CCf, similarly, there was a significant difference was found between reference and WG +1 classes before adjustment: OR=1.45 [95% CI = 1.02 to 2.07; p= 0.041]. However, we noted a disappearance of statistical significance after adjustment: OR=1.44 [95% CI 0.98 to 2.11; p=0.060]. Focus on LGA showed that WG +1 had 1.51-fold higher risk to present a LGA fetus: OR=1.51 [95% CI = 1.07 to 2.13; p=0.018] and this risk persist after adjustment: OR=1.47 [95% CI = 1.02 to 2.11; p=0.038]. Concerning the WG -1 category, no statistical association with the various composite criteria was highlighted (p> 0.05).

4) DISCUSSION:

The aim of this study was to define whether gestational weight gain could be an explanatory factor for maternal and fetal adverse events during pregnancy in women with type 1 diabetes. In this large monocentric cohort of type 1 pregestational diabetes, we found that more than half of the mothers and around 2/3 of the newborns presented a morbidity criterion during these type 1 diabetes pregnancies. Furthermore, more than half women presented an excessive GWG. We have equally showed that an excessive GWG could be participle to maternal -fetal morbidity, assessed by our composite criteria. A significant association was found for apparition of LGA.

Trend to obesity rises worldwide. Note that in France, according to EPOPÉ data published in 2016, concerning a sample of the global population (n=13,551), 27.2% of patients are overweight/obese before pregnancy [11]. This trend concerns equally non pregnancy women with type 1 diabetes, which are more frequently in overweight/ obesity. Our population is in accordance with other authors, and other French cohorts. However, pregestational BMI during

pregnancy in T1D is not associated with maternal and fetal morbidity in our center *(see first proposed article)*, reason why we have an interest for the GWG. Excessive GWG is likely to be multifactorial due to increase in insulin doses, recurrent hypoglycemia, lack of exercise and unpredictability of carbohydrates counting. In fact, the continuous changes in insulin sensitivity during pregnancy require frequent adjustments of the insulin-carbohydrate ratio, which are difficult to predict and requires frequent interaction with specialized nurses and dietitians to maintain euglycemia and avoid both hypoglycemia and ketosis.

Our results are in accordance with precedent studies. 49.6 % type 1 diabetes women had a GWG above the IOM guidelines despite our management: physical coaching, dieticians and medical reevaluation during pregnancy. This proportion was slightly lower than ATLANTIC-DIP report, which found an excessive GWG for 64% of 169 type 1 diabetes women. However, this study was carried out in Ireland and for a period extended 2006-2012: an impact of demography and the increasing attention for GWG by diabetologist and gynecologist since 2012, could be explain this difference [12]. Moreover, a meta-analysis of 20 retrospective studies, published in 2018, showed a different proportion of GWG depending on the population studied (across the USA, western Europe and east Asia), but in western Europe, GWG above the IOM guidelines was measured at 51% of all pregnancies [13].

Our results do not demonstrate an association between maternal morbidity and weight gain in T1D pregnancies, assessed by our composite criterion. The composition of this criterion was based on the relevance and reproducibility of the evaluation of these complications. It should be noted that no study to date has evaluated the relationship between retinopathy progression, excess weight, and type 1 diabetes. A study from our center, concerning the same population, had demonstrated a link between metabolic balance and retinopathy during pregnancy [14]. Concerning proteinuria, gravidic hypertension and preeclampsia, our results are in contradiction with subsequent data in the literature. Gutaj P. & al, in their cohort of 165 T1D patients, found an association between excess GWG and the development of preeclampsia. The prevalence of preeclampsia (9.6%) in their study was like ours (11.2%). However, the women who developed preeclampsia had a duration of disease progression of about 17 years, which is higher than ours. A center effect is possible to explain this difference [15]. Persson & al. also showed an association between pre-pregnancy BMI and preeclampsia: OR=7.1 [95%CI 9.91-14.19][16]. In addition, other studies haven't showed difference between GWG less/within/above IOM guidelines and the apparition of preeclampsia [23].

Patients with an excessive GWG have a 1.47-fold higher risk to present a LGA fetus. LGA infants of mothers with diabetes are at increased risk for fetal distress leading to caesarean

section, and obesity, insulin resistance, type 2 diabetes mellitus (T2DM) and cardiovascular compromise in adolescence and adulthood. Bashir & al., in 2019, showed, in a cohort of 110 type 1 pregestational diabetes *vs*. 1419 without diabetes in pregnancy, that an excessive GWG was associated with LGA: OR=4.53 [95% CI 1.42-14.25, p <0.005], with an adjustment on pregestational BMI and HbA1c during pregnancy [17]. Kawakita et al. showed that the prevalence of excessive GWG in a cohort of 293 T1D patients was 53.9%. Women with excessive GWG have required more insulin, and an excessive GWG was associated with higher risk of macrosomia: OR=2.78 [95% CI 1.23-6.30][18]. Normal-weight women with GWG within guidelines experienced a lower LGA prevalence in two cohort of 333 and 358 type 1 diabetes women published by McWorther and al., supporting the importance of adherence to guidelines for GWG to reduce LGA (IOM guidelines) [19]. Shin Y. & al. evaluated the adjusted RR of having an LGA infant, in a pregestational diabetes population, at 1.7 (95% CI 1.5-1.9) for women with excess GWG compared to those with appropriate gain [20]. C.M. Scifres & al. studied a type 1 diabetes population and showed that LGA birth weight occurred in 48 of 114 (42.1%) of women with excess GWG and 5 of 61 (8.2%) of women with recommended weight gain (p<0.001). The association between excess maternal weight gain and LGA birth weight remained significant after adjustment for pre-pregnancy BMI, gestational age at delivery, nulliparity, vascular complications, and HbA1c measurements (adjusted OR=8.9, [95% CI 3.1 to 26.2, p<0.001] [21]. In a cohort of 221 T1D pregnant women, L. Ladfors & al., confirmed that GWG was an independent risk factor for LGA: OR=1.047 [95% CI 1.044 -1.17, p=0.001][22]. At last, A.L. Secher & al., found that a higher GWG is associated with increasing offspring birth weight independent of maternal glycemic control in 115 Danish women with type 1 diabetes [23]. These results are consistent with our results. To resume, our results were like all the literature sus-cited, concerning excessing GWG during type 1 diabetes pregnancies and the risk of LGA [24].

With regard to other neonatal adverse events, we did not find an association between the neonatal composite end point and fetal morbidity during type 1 diabetes. Possibly, the events included are too rare for the composite endpoint to be sensitive enough. However, different studies have shown an association between high pregestational BMI (≥ 30 kg/m^2), not excessive GWG, and the presence of congenital malformations [25]. It should also be noted that the rate of congenital malformations is higher than the general population, and in agreement with other studies focused on the T1D population. Shoulder dystocia appears to be a complication induced by excess fetal weight, which we have shown to be associated with excess maternal weight (see above). However, some authors have reported the absence of association between excess GWG and this complication. In 2014, Scifres & al. showed no association between neonatal respiratory distress and excess weight in T1D pregnancies [21].

Finally, transfers to neonatal intensive care unit do not appear to be associated with GWG in this cohort. However, the results must be handled with caution because the indications for transfer vary according to the centers and the habits of each team.

Concerning women with a weight gain lower than the recommendations, no statistically significant association was highlighted. In 2021, H. Xu & al., showed a reduction in the risk of caesarean section but without any other reduction concerning maternal-fetal complications [26]. For Kominiarek MA & al., a gestational weight gain below recommendations was associated with spontaneous preterm birth (adjusted OR=1.50 [95% CI 1.31-1.73]) and indicated preterm birth (adjusted OR=1 .34 [95% CI 1.12-1.60])[27]. Possibly, our population was too small to demonstrate a statistical effect.

Several strengths confirm the interest of this work: the large sample size of type 1 diabetes women (most important one-place French longitudinal cohort), the detailed pregnancy outcomes, evaluation by the same multidisciplinary professionals since the beginning of the structure Diabetes & Pregnancy, and population presented clinical characteristics in accordance with the literature provide a power of statistical analysis. Moreover, with reference to the CONCEPTT study, diabetologic management was evaluated over the years of the collection by the increasingly frequent use of the pump, CGMS or the use of new insulin analogs, reason why an adjustment was carried out for the treatment, but equally on mean HbA1c during pregnancy and the duration of diabetes [28]. However, the particularly long duration and the retrospective design of this study with some missing data; reason why we needed to use an imputation for statistical analyses, could generate a lack of power in the statistical comparisons. Furthermore, some potential limitations require discussion. First, a comparison for insulin required between the GWG classes would have been interesting. Secondly, Cyganek et al observed that women with type 1 diabetes who experienced a pregnancy weighed 2.5 kg more than their pre-pregnancy baseline after a median of 20 months postpartum, suggesting a long-term weight retention with potential metabolic effect [29]. Unfortunately, we don’t have data concerning post-partum weight for explore this parameter. Finally, the retrospective nature did not allow us to identify neonatal hypoglycemia.

In conclusion, about 50% of T1D pregnancies are marked by excessive weight gain. The appearance of a LGA newborn is correlated to this excess of GWG. We also know that pregnancies marked by excessive weight gain are more at risk of complications, especially obstetrical ones. During pregnancy, achieving an ideal GWG appears to be as necessary as maintaining good metabolic control for women with type 1 diabetes. To be able to decrease the prevalence of excessive GWG, diabetologists and gynecologists should probably have a

stricter management. Prospective studies will be needed to identify the optimal approach to weight management in women with type 1 diabetes during pregnancy.

5) TABLES & FIGURES :

Figure 1: Patient enrollment flow-chart

Table 1: Baseline maternal characteristics

Table 2: Maternal and fetal characteristics and outcomes, all weights combined

Table 4: Association between adverse maternal/fetal outcomes and weight gain during type 1 diabetes pregnancy

Supplementary Data 4: Comparison of each weight gain category of each BMI classes

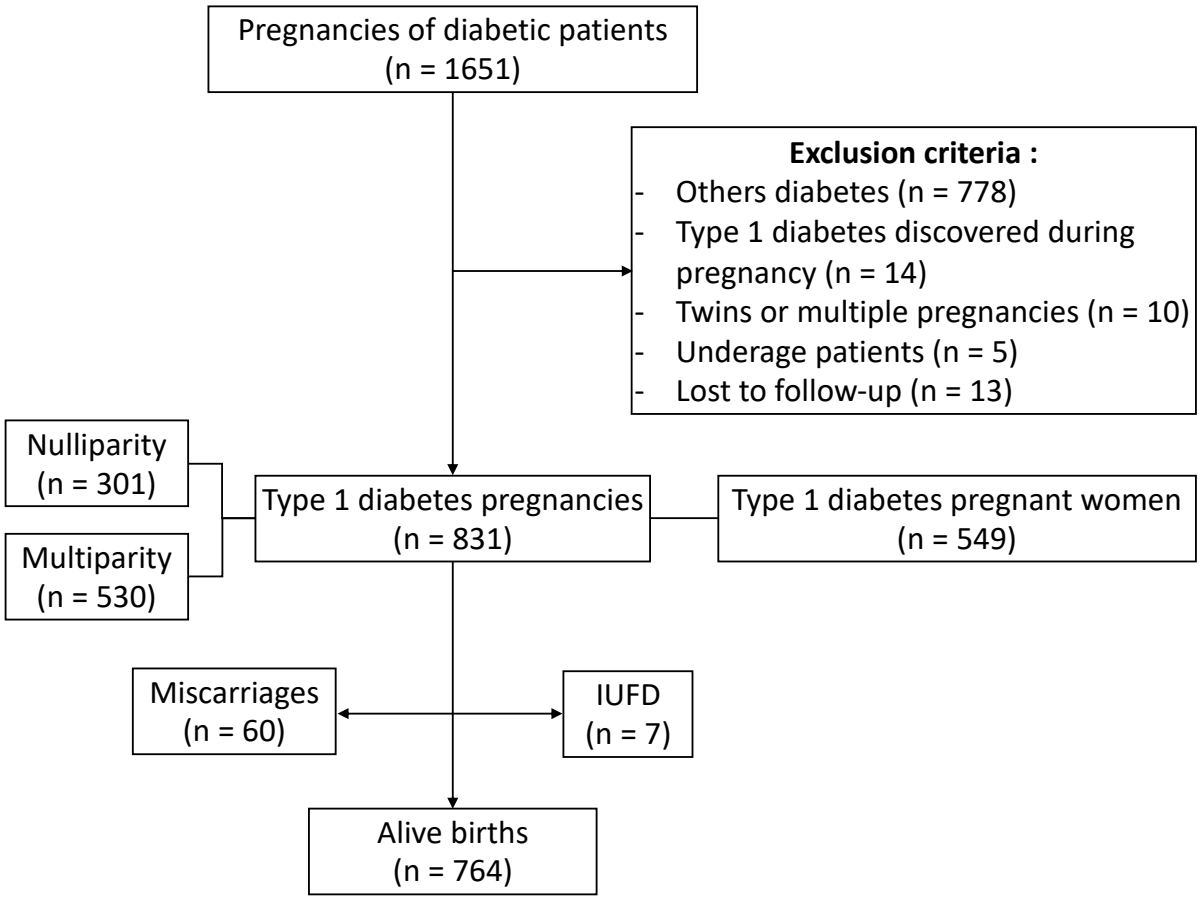

Figure 1 : Patients enrollment flow-chart

Table 1: Baseline maternal characteristics

Maternal characteristics*	**N**	**Values**
Age, years	771	29.4 ± 4.9
Height, m	771	1.65 ± 0.06 [d]
Weight before pregnancy, kg	771	67.41 ± 13.78 [d]
BMI before pregnancy, kg/m²	755	24.85 ± 4.82
Normo-weighted before pregnancy	771	479 (62.1) [d]
Overweighted before pregnancy	771	188 (24.4) [d]
Obese before pregnancy	771	104 (13.5) [d]
Smoking before pregnancy	604	171 (28.3)
Smoking during pregnancy	580	95 (16.4)
Duration of diabetes, years	769	14 (8 ; 20)
Continuous subcutaneous insulin infusion	771	456 (59.1)
FIT before pregnancy	771	228 (29.6)
HbA1c before pregnancy, %, mmol/mol	690	7.15 (6.6 ; 8), 54.6 (48.6 ; 63.9)
HbA1c below 6.5% before pregnancy	690	126 (18.3)
No complication	768	541 (70.4)
Diabetic retinopathy	771	200 (25.9)
Diabetic nephropathy	771	54 (7)
Hypertension	771	30 (3.9)
Nulliparity	771	279 (36.2)

Values are expressed as number (%), or mean ± SD, or median (IQR)
SD: standard deviation, IQR: interquartile range
BMI: body mass index
FIT: functional insulin therapy
IUFD: intrauterine fetal death

* : including IUFD
[d] : after multiple imputation

Table 2: Maternal and fetal characteristics and outcomes, all weights combined

	N	Values	After multiple imputation (N = 771)*
Maternal outcomes			
1st trimester HbA1c, %, mmol/mol	689	6.87 ± 1.07, 51.6 ± 8	6.91 ± 1.09, 52 ± 8.2
2nd trimester HbA1c, %, mmol/mol	715	6.42 ± 0.80, 46.7 ± 5.8	6.42 ± 0.80, 46.7 ± 5.8
3rd trimester HbA1c, %, mmol/mol	650	6.50 ± 0.81, 47.5 ± 5.9	6.54 ± 0.85, 48 ± 6.2
HbA1c during pregnancy, %, mmol/mol	715	6.47 (6.03 ; 6.97), 47.2 (42.4 ; 52.7)	
Diabetic retinopathy evolved	736	195 (26.5)	206 (26.7)
Proteinuria evolved	765	181 (23.7)	184 (23.8)
Gravidic hypertension	765	129 (16.9)	131 (17.0)
Preeclampsia	765	90 (11.8)	92 (11.9)
Vaginal delivery	766	389 (50.8)	
Labor induction before successful vaginal delivery	389	285 (73.3)	
Operative vaginal delivery	389 [a]	163 (41.9) [a]	
	766 [c]	163 (21.2) [c]	
Cesarean section	766	377 (49.2)	
Emergency cesarean section before labour	366 [b]	84 (23) [b]	
	764 [c]	84 (11) [c]	
Postpartum hemorrhage	682	59 (8.7)	85 (11.0)
Ketoacidosis during pregnancy	771	24 (3.1)	24 (3.1)
Intensive Care Unit admission	771	9 (1.2)	
Maternal composite criterion	711	386 (54.3)	404 (52.3)
Fetal outcomes			
Term, weeks	769	38 (37 ; 38.4)	
Prematurity	769	164 (21.3)	166 (21.5)
Male	767	392 (51.1)	
Birth weight, grams	758	3507 ± 678	
Macrosomia	758	173 (22.8)	
LGA	758	402 (53.0)	405 (52.5)
SGA	758	14 (1.9)	23 (3.0)
Severe neonatal malformations	763	59 (7.7)	61 (7.9)
Shoulder dystocia	742	59 (8.0)	66 (8.5)
Apgar score < 7 at 1 min.	697	68 (9.8)	
Apgar score < 7 at 5 min.	697	19 (2.7)	
Arterial pH < 7.15	533	133 (24.5)	
Arterial pH < 7	533	13 (2.4)	
Respiratory distress	740	70 (9.5)	74 (9.6)
Neonatal Intensive Care Unit Admission	751	104 (13.8)	110 (14.3)
IUFD	771	7 (0.9)	7 (0.9)
Fetal composite criterion	759	524 (69.0)	529 (68.6)

Values are n (%/total), mean ± SD, median (IQR)
SD: standard deviation, IQR: interquartile range
LGA: large for gestational age
SGA: small for gestational age
IUFD: intrauterine fetal death

Maternal composite criterion: at least 1 complication among diabetic retinopathy, proteinuria, gravidic hypertension, preeclampsia, postpartum hemorrhage or ketoacidosis
Fetal composite criterion: at least 1 complication among prematurity, LGA, SGA, shoulder dystocia, severe malformations, respiratory distress or intensive care unit admission
These criteria are positive if at least one of the elements is present

* : including intrauterine fetal deaths
[a] : vaginal deliveries only
[b] : cesarean sections only
[c] : all deliveries included

Table 4: Association between adverse maternal/fetal outcomes and weight gain during type 1 diabetes pregnancy

	Complications		Unadjusted		Adjusted	
	No	Yes	Odds Ratio (95%CI)	p	Odds Ratio (95%CI)	p
Maternal CC	N = 368	N = 403				
Gest. weight gain				0.038		0.11
-1	75 (20.27)	67 (16.58)	0.98 (0.62 to 1.53)	0.92	1.03 (0.63 to 1.68)	0.90
0	127 (34.67)	117 (29.06)	1.00 (ref.)	-	1.00 (ref.)	-
+1	166 (45.06)	219 (54.37)	1.44 (1.03 to 2.01)	**0.033**	1.40 (0.98 to 2.01)	0.065
Mean ± SD	13.76 ± 5.18	14.37 ± 5.28	1.02 (0.99 to 1.05)	0.12	1.02 (0.99 to 1.06)	0.15
Fetal CC	N = 243	N = 528				
Gest. weight gain				0.076		0.13
-1	50 (20.54)	91 (17.33)	1.01 (0.65 to 1.57)	0.6	1.02 (0.63 to 1.67)	0.91
0	87 (35.80)	158 (29.85)	1.00 (ref.)	-	1.00 (ref.)	-
+1	106 (43.66)	279 (52.82)	1.45 (1.02 to 2.07)	**0.041**	1.44 (0.98 to 2.11)	0.060
Mean ± SD	13.54 ± 4.93	14.33 ± 5.36	1.03 (1.00 to 1.06)	**0.062**	1.03 (1.00 to 1.07)	**0.050**
LGA	N = 366	N = 405				
Gest. weight gain				< 0.001		0.002
-1	85 (23.31)	56 (13.85)	0.68 (0.44 to 1.05)	0.083	0.66 (0.41 to 1.05)	0.079
0	124 (33.97)	120 (29.70)	1.00 (ref.)	-	1.00 (ref.)	-
+1	157 (42.71)	229 (56.46)	1.51 (1.07 to 2.13)	**0.018**	1.47 (1.02 to 2.11)	**0.038**
Mean ± SD	13.30 ± 5.18	14.79 ± 5.20	1.06 (1.02 to 1.09)	**< 0.001**	1.06 (1.03 to 1.10)	**< 0.001**

Values are n (%)
SD: standard deviation
LGA: large for gestational age
CC: composite criterion
CSII: continuous subcutaneous insulin infusion
IOM: Institute of Medecine

Gestational weight gain: -1 = below IOM recommendations (2009) ; 0 = within IOM recommendations ; +1 = above IOM recommendations

Adjustments were made for mean HbA1c during pregnancy, year of delivery and type of treatment (insulin versus CSII)

Maternal composite criterion: at least 1 complication among diabetic retinopathy, proteinuria, gravidic hypertension, preeclampsia, postpartum hemorrhage or ketoacidosis

Fetal composite criterion: at least 1 complication among prematurity, LGA, SGA, shoulder dystocia, severe malformations, respiratory distress or intensive care unit admission

These criteria are positive if at least one of the elements is present

Supplementary data 4: Comparison of each weight gain category for each BMI classes

	BMI classes								
	Class 1			Class 2			Class 3		
	GWG below reco. n=108/426 (25.4%)	GWG within reco. n=154/426 (36.2%)	GWG above reco. n=164/426 (38.5%)	GWG below reco. n=11/176 (6.2%)	GWG within reco. n=44/176 (25%)	GWG above reco. n=121/176 (68.8%)	GWG below reco. n=9/95 (9.5%)	GWG within reco. n=21/95 (22.1%)	GWG above reco. n=65/95 (68.4%)
Pre-pregnancy characteristics									
Smoking before pregnancy	26.5 (22/83)	26.8 (34/127)	38.5 (50/130)	20 (2/10)	13.8 (4/29)	31.4 (33/105)	0 (0/5)	22.2 (4/18)	12.7 (7/55)
Duration of diabetes, years	14 (8 to 21)	14 (8 to 21)	13 (7 to 19)	13 (6 to 22)	14 (9 to 17)	15 (10 to 20)	15.5 (6.5 to 19)	15 (7 to 19)	17 (12 to 22)
CSII	57.3 (63/110)	59.4 (95/160)	51.5 (86/167)	45.5 (5/11)	63.6 (28/44)	64.4 (76/118)	87.5 (7/8)	66.7 (14/21)	74.2 (49/66)
HbA1c before pregnancy, %	7.21 ± 1.32	7.43 ± 1.53	7.68 ± 1.51	7.71 ± 1.32	7.34 ± 1.17	7.86 ± 1.66	8.2 ± 1.46	7.41 ± 1.22	7.52 ± 1.22
HbA1c < 6,5 % before pregnancy	29.7 (30/101)	20.9 (29/139)	18.2 (28/154)	12.5 (1/8)	7.1 (3/42)	12.8 (14/109)	0 (0/7)	26.3 (5/19)	10 (6/60)
No complication	74.5 (82/110)	71.3 (114/160)	70.7 (118/167)	72.7 (8/11)	72.7 (32/44)	61.9 (73/118)	87.5 (7/8)	81 (17/21)	69.7 (46/66)
Diabetic retinopathy	24.5 (27/110)	25 (40/160)	27.5 (46/167)	18.2 (2/11)	22.7 (10/44)	32.2 (38/118)	0 (0/8)	14.3 (3/21)	24.2 (16/66)
Diabetic nephropathy	6.4 (7/110)	5.6 (9/160)	4.8 (8/167)	18.2 (2/11)	6.8 (3/44)	11.9 (14/118)	12.5 (1/8)	0 (0/21)	7.6 (5/66)
Hypertension	5.5 (6/110)	1.9 (3/160)	4.2 (7/167)	9.1 (1/11)	2.3 (1/44)	1.7 (2/118)	0 (0/8)	0 (0/21)	10.6 (7/66)
Maternal outcomes									
HbA1c during pregnancy, %	6.47 ± 0.95	6.45 ± 0.76	6.60 ± 0.70	6.62 ± 0.81	6.55 ± 0.58	6.81 ± 0.77	6.62 ± 0.76	6.42 ± 0.77	6.62 ± 0.66
Diabetic retinopathy evolved	20.8 (22/106)	27 (41/152)	29.6 (48/162)	9.1 (1/11)	19.5 (8/41)	31 (36/116)	37.5 (3/8)	21.1 (4/19)	32.8 (21/64)
Gravidic hypertension	15.6 (17/109)	13.1 (21/160)	17.4 (29/167)	18.2 (2/11)	7 (3/43)	16.1 (19/118)	12.5 (1/8)	28.6 (6/21)	22.7 (15/66)
Proteinuria evolved	16.5 (18/109)	20 (32/160)	28.1 (47/167)	18.2 (2/11)	11.6 (5/43)	28 (33/118)	25 (2/8)	23.8 (5/21)	27.3 (18/66)
Preeclampsia	9.2 (10/109)	8.8 (14/160)	13.2 (22/167)	18.2 (2/11)	7 (3/43)	16.1 (19/118)	12.5 (1/8)	33.3 (7/21)	22.7 (15/66)
Cesarean section	40.9 (45/110)	39.4 (63/160)	50.6 (84/166)	27.3 (3/11)	56.8 (25/44)	59.8 (70/117)	71.4 (5/7)	47.6 (10/21)	64.6 (42/65)
Emergency cesarean section	31.1 (14/45) [a] ;	14.3 (9/63) [a] ;	17.9 (15/84) [a] ;	100 (3/3) [a] ;	16 (4/25) [a] ;	25.7 (18/70) [a] ;	20 (1/5) [a] ;	20 (2/10) [a] ;	28.6 (12/42) [a] ;
before labour	12.7 (14/110) [c]	5.6 (9/160) [c]	9 (15/166) [c]	27.3 (3/11) [c]	9.1 (4/44) [c]	15.4 (18/117) [c]	14.3 (1/7) [c]	9.5 (2/21) [c]	18.8 (12/64) [c]
Operative vaginal delivery	33.8 (22/65) [b] ; 20 (22/110) [c]	39.2 (38/97) [b] ; 23.8 (38/160) [c]	58.5 (48/82) [b] ; 28.9 (48/166) [c]	37.5 (3/8) [b] ; 27.3 (3/11) [c]	26.3 (5/19) [b] ; 11.4 (5/44) [c]	57.4 (27/47) [b] ; 23 (27/117) [c]	0 (0/2) [b] ; 0 (0/7) [c]	45.5 (5/11) [b] ; 23.8 (5/21) [c]	30.4 (7/23) [b] ; 10.8 (7/65) [c]
Postpartum hemorrhage	9.4 (9/96)	8.4 (12/143)	4.3 (6/141)	11.1 (1/9)	11.9 (5/42)	7.6 (8/105)	0 (0/6)	0 (0/20)	16.7 (10/60)
Ketoacidosis during pregnancy	4.5 (5/110)	3.1 (5/160)	3.6 (6/167)	0 (0/11)	0 (0/44)	2.5 (3/118)	0 (0/8)	4.8 (1/21)	1.5 (1/66)
Intensive Care Unit Admission	0.9 (1/110)	0.6 (1/160)	0.6 (1/167)	0 (0/11)	0 (0/44)	2.5 (3/118)	0 (0/8)	0 (0/21)	0 (0/66)
Fetal outcomes									
Prematurity	28.2 (31/110)	18.8 (30/160)	16.8 (28/167)	63.6 (7/11)	15.9 (7/44)	16.1 (19/118)	12.5 (1/8)	33.3 (7/21)	22.7 (15/66)
Birth weight, grams	3292 ± 691	3448 ± 574	3656 ± 601	2946 ± 1200	3580 ± 585	3688 ± 634	3338 ± 433	3421 ± 784	3522 ± 579
Macrosomia	13.6 (15/110)	16.5 (26/158)	27.7 (46/166)	9.1 (1/11)	29.5 (13/44)	29.3 (34/116)	12.5 (1/8)	28.6 (6/21)	20.3 (13/64)
LGA	41.8 (46/110)	46.2 (73/158)	62 (103/166)	36.4 (4/11)	52.3 (23/44)	62.9 (73/116)	25 (2/8)	61.9 (13/21)	50 (32/64)
SGA	2.7 (3/110)	2.5 (4/158)	0 (0/166)	0 (0/11)	4.5 (2/44)	0.9 (1/116)	0 (0/8)	0 (0/21)	3.2 (2/63)
Severe neonatal malformations	5.5 (6/110)	8.2 (13/159)	7.8 (13/167)	9.1 (1/11)	9.1 (4/44)	4.2 (5/118)	0 (0/8)	14.3 (3/21)	6.3 (4/64)
Shoulder dystocia	5.6 (6/107)	8.3 (13/156)	12.8 (21/164)	10 (1/10)	2.3 (1/43)	6.9 (8/116)	0 (0/6)	0 (0/20)	11.3 (7/62)
Apgar score < 7 at 1 min.	10 (10/100)	4.1 (6/147)	9.8 (15/153)	9.1 (1/11)	12.5 (5/40)	13 (14/108)	0 (0/6)	10 (2/20)	15.5 (9/58)
Apgar score < 7 at 5 min.	3 (3/100)	0.7 (1/147)	3.9 (6/153)	0 (0/11)	5 (2/40)	1.9 (2/108)	0 (0/6)	5 (1/20)	3.4 (2/58)
Arterial pH < 7.15	17.1 (12/70)	19 (22/116)	25.2 (28/111)	22.2 (2/9)	18.2 (6/33)	22.9 (19/83)	20 (1/5)	33.3 (6/18)	41.7 (20/48)
Arterial pH < 7	1.4 (1/70)	3.4 (4/116)	3.6 (4/111)	0 (0/9)	0 (0/33)	0 (0/83)	0 (0/5)	0 (0/18)	4.2 (2/48)
Respiratory distress	13.2 (14/106)	6.4 (10/156)	7.9 (13/164)	10 (1/10)	9.3 (4/43)	8.6 (10/116)	0 (0/6)	10 (2/20)	14.8 (9/61)
Neonatal ICU Admission	18.7 (20/107)	9.6 (15/157)	13.3 (22/166)	27.3 (3/11)	20.5 (9/44)	12.8 (15/117)	0 (0/8)	9.5 (2/21)	16.1 (10/62)

Values are % (n/total), or mean ± SD, or median (IQR)
CSII: continuous subcutaneous insulin infusion
SD: standard deviation, IQR: interquartile range
ICU: Intensive Care Unit
GWG: gestational weight gain
LGA: Large for Gestational Age
SGA: Small for Gestational Age
[a]: cesarean section only
[b]: vaginal deliveries only
[c]: all deliveries included
Class 1: BMI < 25 kg/m², class 2: BMI ≥ 25 and < 30 kg/m², class 3: BMI ≥ 30 kg/m²

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V. PERSPECTIVES :

Notre étude a mis en évidence une corrélation positive entre l'excès de prise de poids gestationnelle et la survenue d'une croissance fœtale excessive pouvant engendrer un excès de morbidité materno-fœtale. À défaut d'avoir des recommandations spécifiques pour les grossesses de femmes diabétiques, nous nous sommes basés sur les recommandations de l'IOM, qui sont les plus communément admises, rendant nos données comparables aux études traitant cette problématique.

En revanche, nous n'avons pas montré de lien significatif entre une augmentation de l'IMC pré-gestationnel et la survenue des complications maternelles ou fœtales que nous vous avons présenté sous forme de critère composite. Ce résultat est critiquable sur divers points :

1. Conception des critères composites, qui semblent finalement trop peu discriminants entre les classes pondérales. À l'avenir, nous pourrions en modifier la composition, avec par exemple un critère lié aux complications vasculaires (microangiopathie, HTA gravidique, prééclampsie), aux complications obstétricales (césarienne, hémorragie du post-partum), aux complications fœtales lors de l'accouchement (macrosomie, dystocie des épaules), aux complications fœtales immédiates (détresse respiratoire, score d'Apgar <7, transfert en réanimation néonatale) ou aux complications néonatales métaboliques (hypocalcémie, hypoglycémie, ictère, pH < 7.15). Les possibilités sont nombreuses et pourraient ainsi s'adresser plus spécifiquement aux gynécologues, obstétriciens/sage-femme ou diabétologues. La définition de critère composite idéal semble être la clé et sera l'objectif de futures investigations.
2. Aspect rétrospectif menant à diverses données manquantes pour lesquelles des imputations ont été nécessaires. La mise en place de cohortes prospectives nous permettrait de s'amender de ces difficultés.

Avec ces résultats, nous rappelons l'importance d'un suivi pondéral au cours des grossesses de femmes diabétiques de type 1. La mesure de poids est facile, rapide, et pourrait s'effectuer au domicile à l'aide de balance connectée, permettant un suivi digitalisé directement en lien avec le service prenant en charge la patiente.

De plus, nous disposons de la plus grande cohorte monocentrique française de grossesses diabétiques de type 1. Les avancées technologiques ont modifié les systèmes de surveillance

glycémique et les techniques d'administration de l'insuline, alors que l'organisation du suivi et les protocoles obstétricaux ont peu évolué depuis l'inclusion de la première patiente en 1997. Cela nous donne un fort pouvoir statistique, qui nous permettra d'aboutir à de nombreux autres travaux de recherches cliniques, dont le but est toujours d'optimiser la prise en charge des patientes en pratique clinique.

Concernant notre thématique de recherche (poids-excès de poids au cours de la grossesse), nous n'avons pas pu analyser l'impact des efforts entrepris par les patientes au cours de la grossesse. Une femme en surpoids initial a-t-elle les mêmes risques materno fœtaux si elle perd 5 ou si elle prend 5 kg au cours de la grossesse ? Surtout, est-ce que si cette perte de poids est effective au 1er trimestre, y a-t-il de meilleures issues de grossesses en comparaison à une perte de poids qui aurait lieu au 3ème trimestre ? D'autres analyses issues de notre base de données seront nécessaires pour répondre à ces questions dont l'utilité clinique pourrait être indéniable.

À l'instar des grandes cohortes scandinaves issues de registres nationaux, il serait intéressant de rajouter des informations économico-sociales dans de futures analyses, tant la problématique pondérale est intimement liée au mode vie des patientes. Cela ne pourra se faire qu'au gré de cohortes prospectives.

Enfin, ces complications sont induites par plusieurs mécanismes physiopathologiques complexes et mal connus. Plusieurs facteurs confondants persistent : tabac, profil sportif, ... par exemple. On peut également citer les troubles du métabolisme lipidique et l'anémie maternelle. En raison du caractère rétrospectif de notre étude, nous n'avons pas pu en tenir compte, mais cela peut constituer des pistes pour de futurs travaux.

VI. CONCLUSION :

Notre étude montre que l'excès de prise de poids gestationnelle au cours des grossesses de femmes diabétiques de type 1 semble être un facteur de risque à considérer de manière plus importante que l'IMC pré-gestationnel dans la survenue des complications materno-fœtales.

Ces résultats confirment l'importance de la surveillance pondérale au cours de ces grossesses à risque, dont l'enjeu concerne à la fois la santé de la future mère, le bon développement du fœtus puis la croissance du nouveau-né. Cet intérêt porté sur le poids doit ainsi concerner le diabétologue, le gynécologue-obstétricien, la sage-femme mais aussi la femme
enceinte, et doit commencer dès l'expression de son souhait de grossesse.

En effet, la grossesse chez les femmes diabétiques de type 1 se caractérise par un risque important de multiples complications, comme nous l'avons démontré tout au long de cette étude, pour laquelle la future mère doit se préparer en étant accompagnée par une équipe expérimentée et attentive. De plus, une compréhension et une coopération de la patiente sont indissociables pour une correction efficace d'un excès de prise de poids, par le biais de modifications de son mode vie adaptées au stade de la grossesse, associant mesures diététiques et maintien d'une activité physique. L'efficacité d'une telle prise en charge est démontrée chez les femmes non-diabétiques, avec une réduction significative de la prise de poids associant, pour tout IMC pré-gestationnel, une moindre incidence de l'HTA gravidique, de la césarienne et de la détresse respiratoire néonatale, ainsi qu'une diminution de la macrosomie chez les femmes obèses [30].

En ce sens, l'ensemble de ces données encourage nos efforts en démontrant qu'il est possible de diminuer les risques de morbidité encourus par les femmes diabétiques de type 1 lors de leur grossesse.

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Date de soutenance : 22 avril 2022

Titre de la thèse : Impact de l'IMC pré-gestationnel et de la prise de poids gestationnelle sur les complications materno-fœtales au cours de grossesses de patientes diabétiques de type 1

Thèse - Médecine - Lille 2022

Cadre de classement : *Diabétologie*

DES : *Endocrinologie diabétologie, nutrition*

Mots-clés : Diabète de type 1, IMC pré-gestationnel, prise de poids gestationnelle, grossesse

Contexte et objectif : À l'instar de l'augmentation de l'incidence du surpoids et de l'obésité, les patientes diabétiques de type 1 débutent leur grossesse de plus en plus fréquemment en condition de surcharge pondérale. L'excès pondéral préexistant à la grossesse et/ou per-partum est connu pour être un facteur de risque de survenue de nombreuses complications durant les grossesses de femmes non-diabétiques. Notre objectif était de définir les impacts respectifs de l'IMC pré-gestationnel et de l'excès de prise de poids (PPG) sur l'apparition de complications materno-fœtales au cours de grossesses de diabétiques de type 1.

Matériel et méthodes : Étude observationnelle, rétrospective, monocentrique menée au sein de la maternité Jeanne de Flandres (CHRU, Lille). Nous avons recueilli les données métaboliques et les complications maternelles et fœtales chez l'ensemble des patientes diabétiques de type 1 enceintes suivies entre 1997 et 2021. Une première étude concerne l'analyse de l'IMC pré-gestationnel : classe 1 si IMC < 25 kg/m^2 (poids normal), classe 2 si IMC ≥ 25 et < 30 kg/m^2 (surpoids) et classe 3 si IMC ≥ 30 kg/m^2 (obésité). Une seconde étude analyse l'impact de la prise de poids au cours de la grossesse, en fonction de son adéquation avec les recommandations proposées par l'Institute of Medecine en 2009 : les grossesses sont réparties en catégories Weight Gain (WG) -1 (PPG inférieure), WG 0 (PPG en adéquation), ou WG +1 (PPG supérieure). Nous avons défini un critère composite maternel (CCm), considéré positif si au moins un des éléments suivants était présent : rétinopathie diabétique, protéinurie, hypertension gravidique, prééclampsie, hémorragie du post-partum et décompensation céto-acidosique. De même, nous avons utilisé un critère composite fœtal (CCf), considéré positif si au moins un des éléments suivants était présent : LGA (Large for Gestational Age), SGA (Small for Gestational Age), prématurité, dystocie des épaules, malformations congénitales, détresse respiratoire aiguë précoce et transfert en réanimation néonatale. Les critères LGA, prématurité et prééclampsie ont également été analysés isolément dans la partie concernant l'IMC pré-gestationnel, alors que seul le critère LGA a été analysé isolément dans la partie concernant la PPG. Les résultats sont exprimés en Odds Ratio (OR) et leurs intervalles de confiance (CI) à 95%.

Résultats : Un total de 771 grossesses de diabétiques de type 1 a été analysé, dont 764 naissances vivantes. L'âge moyen était de 29.4 ± 4.9 ans, avec un IMC pré-gestationnel moyen à 24.85 ± 4.82 kg/m^2. 36.2% étaient nullipares. L'HbA1c médian pré-gestationnel était de 7.15 % (6.60 ; 8), avec une ancienneté médiane du diabète de 14 ans (8 ; 20). 70.4% des patientes n'avaient pas de complication liée au diabète avant leur grossesse. Les grossesses étaient marquées par la survenue de rétinopathie diabétique (26.7%), protéinurie (23.9%), HTA gravidique (17%) et prééclampsie (11.9%). La césarienne urgente et l'hémorragie du post-partum ont été comptabilisées toutes deux lors de 11% de l'ensemble des accouchements. Une décompensation céto-acidosique est retrouvée lors de 9 grossesses (1.2%). Le terme médian était de 38 semaines d'aménorrhée (37 ; 38.4), avec un taux de prématurité de 21.5%. Le poids moyen à la naissance était de 3507 ± 678 grammes, avec un taux de LGA à 52.5%, de macrosomie à 22.8% et de SGA à 3%. 8.6% des accouchements étaient marqués par une dystocie des épaules. Parmi ces nouveau-nés, 7.9% présentaient une malformation congénitale, 9.6% une détresse respiratoire aiguë et 14.3% ont été transférés en réanimation néonatale. Les CCm et CCf étaient retrouvés respectivement dans 52.4% et 68.6% des grossesses. Après répartition selon l'IMC pré-gestationnel, 62.1% des femmes étaient normopondérées (C1), 24.4% en surpoids (C2) et 13.5% obèses (C3). Le calcul des OR pour les critères composites, LGA, prématurité et prééclampsie n'a pas montré de différence significative entre ces classes pondérales au sein de notre cohorte, malgré une tendance en faveur d'une augmentation du risque pour les classes C2 et C3. Selon les recommandations de PPG, 18.3% des grossesses ont une PPG inférieure aux recommandations (WG -1), 31.1% ont une PPG correcte (WG 0) et 49.6% ont une PPG supérieure aux recommandations (WG +1). Pour le CCm, nous avons montré une différence significative entre WG +1 et WG 0 (référence), avec OR=1.44 [95% CI=1.03 to 2.01; p=0.033] avant ajustement, puis une disparition de cette significativité après ajustement : OR=1.40 [95% CI=0.98 to 2.01; p=0.06]. De même, pour le CCf, OR=1.45 [95% CI=1.02 to 2.07; p= 0.041] avant ajustement, puis OR=1.44 [95% CI=0.98 to 2.11; p=0.060] après ajustement. Le critère LGA était significativement lié à l'excès de PPG (WG +1), avec un OR=1.47 [95% CI=1.02 to 2.11; p=0.038] après ajustement.

Conclusion : L'excès de prise de poids gestationnelle au cours de grossesses de femmes diabétiques de type 1 semble être un facteur de risque plus important que l'IMC pré-gestationnel dans la survenue des complications materno-fœtales, appréciées sous la forme de nos critères composites. Ces résultats confirment l'importance de la surveillance pondérale au cours de ces grossesses à risque, dont l'enjeu concerne à la fois la santé de la future mère, le bon développement du fœtus puis la croissance du nouveau-né.

Composition du Jury :

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