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Association entre l'HBA1c et les complications materno-foetales au cours du diabète de type 2

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AVERTISSEMENT

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Liste des abréviations

ADA : American Diabetes Association
BMI : Body Mass Index
CHRU : Centre Hospitalier Régional Universitaire
CI : Confidence Interval
CGMS : Continuous Glucose Monitoning Sensor
CNGOF : Collège National des Gynécologues et Obstétriciens Français
CSII : Continuous Subcutaneous Insulin Infusion
DT1/T1D : Diabète de type 1
DT2/T2D : Diabète de type 2
HbA1C : Hémoglobine glycquée
HTA : Hypertension artérielle
NICU : Neonatal Intensive Care Unit
IQR : Interquartile Range
IUFD: Intra Uterine Fetal Death
LGA: Large for Gestational Age
OMS : Organisation Mondiale de la Santé
OR : Odds Ratio
RR : Relative Risk
SD : Standard Deviation
SFD : Société Francophone de Diabétologie
SGA : Small for Gestational Age
WHO : World Health Organization

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I- RÉSUMÉ :

Contexte et objectif : Malgré l'optimisation de la prise en charge au cours de la grossesse, les diabétiques de type 2 (DT2) présentent un risque toujours supérieur de complications maternelles et foetales**.** L'objectif était d'évaluer l'impact de l'équilibre glycémique, objectivé par l'HbA1C des 1er et 3e trimestre, sur les complications maternelles et fœtales au cours des grossesses de patientes DT2.

Matériels et Méthodes : Étude observationnelle, monocentrique, rétrospective, conduite à la maternité Jeanne de Flandres (CHU de Lille) entre 1997 et 2021. Nous avons recueilli les données métaboliques, les complications maternelles obstétricales, fœtales et néonatales au cours des grossesses de DT2. Après description des évènements indésirables de grossesse (pré-éclampsie, LGA, SGA, prématurité, malformations congénitales, transferts en réanimation néonatale), nous avons étudié leur association avec l'équilibre glycémique (HbA1C 1er et 3ème trimestre). Enfin nous avons réalisé une analyse en sous-groupes d'équilibre métabolique afin d'étudier l'association entre la cinétique d'HbA1c au cours de la grossesse et les complications materno-foetales. Les résultats ont été exprimés en odds ratios (OR) et leurs intervalles de confiance (IC) à 95 %.

Résultats : 583 patientes DT2 ont donné naissance à un enfant unique, vivant, au cours de la période d'étude. L'âge moyen était de 33.9 ± 5.4 ans, l'IMC prégestationnel était de 34.9 ± 7.10 kg/m2 avec une prise de poids totale moyenne au cours de la grossesse *de* 8.0kg (3.0-12.0). L'HbA1C moyenne du premier trimestre était de 6.33 ± 0.99% et celle du troisième trimestre de 5.93 ± 0.75 %. La durée d'évolution médiane du diabète était de 2.0 ans (0.0-5.0). 82.7% des femmes étaient multipares. Les

grossesses étaient marquées par la survenue de 12.0% d'HTA gravidique, 7.9% de prééclampsie, 11.0% de protéinurie. Les naissances par césariennes représentaient 49.4% des accouchements d'un terme médian de 38 semaines d'aménorrhée (37.6-38.9). Le poids moyen des nouveaux-nés était de 3329 ± 688 grammes. Le taux de prématurité était de 15.6%, celui des transferts en réanimation néonatale de 12.2% et de malformations congénitales de 5.3%. 29.2% des nouveaux nés étaient LGA et 7.9% SGA. 1.4% des naissances étaient marquées par une dystocie des épaules.

L'HbA1C du premier trimestre est associée au LGA (OR 1.33 ; 95%IC 1.09 -1.62 ; p=0.004), à la prématurité (OR 1.39 ; 95%IC 1.11 -1.75 ; p=0.004), à la césarienne (OR 1,66 ; 95%IC 1.11 -2.48 ; p=0.014) et au transfert en réanimation néonatale (OR 1.33 ; 95%IC 1.75 -2.29 ; p<0.001). L'HbA1C du troisième trimestre est associée au LGA (OR 2.67 ; 95%IC 1.75 -4.07 ; p<0.001), à la césarienne (OR 1.30 ; 95%IC 1.02 -1.66 ; p=0.031) et au transfert en réanimation néonatale (OR 1.43 ; 95%IC 1.02 -2.01 ; p=0.038). L'analyse en sous-groupe d'équilibre métabolique retrouve qu'en cas de déséquilibre précoce, pour chaque augmentation de 0,1 % de l'HbA1c au 1er trimestre, les risques de prématurité (OR 1.39 ; 95%IC 1.11 -1.75 ; p=0.004) et d'admission en réanimation néonatale (OR 1.75 ; 95%IC 1.33 -2.29 ; p<0.001) augmentent. En cas de déséquilibre tardif, pour chaque augmentation de 0,1 % de l'HbA1c au 3ème trimestre, le risque de LGA est majoré (OR 2.67 ; 95%IC 1.75 -4.07 ; p<0.001).

Conclusions : L'HbA1C du 1er mais également du 3ème trimestre est associée aux complications materno-fœtale au cours des grossesses DT2. En cas de déséquilibre glycémique précoce, l'élévation de l'HbA1C du 1er trimestre est associé à un sur-risque de transfert en unité de Réanimation néonatale et de prématurité, malgré la correction de l'équilibre glycémique avant le 3ème trimestre. En cas de déséquilibre tardif, le

niveau d'HbA1c est un marqueur du risque de LGA. Ces résultats confirment la nécessité d'obtenir un équilibre glycémique strict pendant toute la grossesse mais également l'importance de la préparation pré-conceptionnelle.

Mots clés : Diabète de type 2, grossesse, équilibre glycémique, HbA1C, complication materno-fœtale.

ABSTRACT :

Background and objective : Despite the optimization of management during pregnancy, type 2 diabetics (T2DM) still have a higher risk of maternal and fetal complications. The objective was to evaluate the impact of glycemic control, as assessed by HbA1C in the first and third trimesters, on maternal and fetal complications in pregnancies of patients with T2DM.

Research design : Observational, monocentric, retrospective study conducted at the Jeanne de Flandres maternity hospital (Lille University Hospital) between 1997 and 2021. We collected metabolic data, obstetric, fetal and neonatal complications during T2DM pregnancies. After describing the adverse pregnancy events (pre-eclampsia, LGA, SGA, prematurity, congenital malformations, transfers to neonatal intensive care), we studied their association with glycemic control (HbA1C 1st and 3rd trimester). Finally, we performed a subgroup analysis of metabolic control to study the association between HbA1*C* kinetics during pregnancy and maternal-fetal complications. Results were expressed as odds ratios (OR) and their 95% confidence intervals (CI).

Results : 583 T2DM patients gave birth to a live, singleton child during the study period. The mean age was 33.9 ± 5.4 years, the pregestational BMI was 34.9 ± 7.10 kg/m2 with a mean total weight gain during pregnancy of 8.0kg (3.0-12.0). The mean HbA1C in the first trimester was 6.33 ± 0.99% and in the third trimester 5.93 ± 0.75%. The median duration of diabetes was 2.0 years (0.0-5.0). 82.7% of women were multiparous. Pregnancies were marked by the occurrence of 12.0% of severe hypertension, 7.9% of pre-eclampsia, 11.0% of proteinuria. Caesarean sections represented

49.4% of deliveries with a median term of 38 weeks of amenorrhea (37.6-38.9). The mean weight of the newborns was 3329 ± 688 grams. The prematurity rate was 15.6%, the neonatal intensive care unit transfer rate was 12.2% and the congenital malformation rate was 5.3%. 29.2% of newborns were LGA and 7.9% SGA. 1.4% of births were marked by shoulder dystocia. First trimester HbA1C was associated with LGA (OR 1.33; 95%IC 1.09 -1.62; p=0.004), prematurity (OR 1.39; 95%IC 1.11 -1.75; p=0.004), caesarean section (OR 1.66; 95%IC 1.11 -2.48; p=0.014) and transfer to neonatal intensive care unit (OR 1.33; 95%IC 1.75 -2.29; p<0.001) Third-trimester HbA1C was associated with LGA (OR 2.67; 95%IC 1.75 -4.07; p<0.001), cesarean section (OR 1.30; 95%IC 1.02 -1.66; p=0.031), and neonatal intensive care unit transfer (OR 1.43; 95%IC 1.02 -2.01; p=0.038). Metabolic balance subgroup analysis found that in case of early imbalance, for each 0.1% increase in HbA1c in the 1st trimester, the risks of prematurity (OR 1.39; 95%IC 1.11 -1.75; p=0.004) and neonatal intensive care admission (OR 1.75; 95%IC 1.33 -2.29; p<0.001) increased. In case of late imbalance, for each 0.1% increase in HbA1c in the third trimester, the risk of LGA was increased (OR 2.67; 95%IC 1.75 -4.07; p<0.001).

Conclusions: 1st but also 3rd trimester HbA1C is associated with maternal-fetal complications in T2DM pregnancies. In case of early glycemic imbalance, the elevation of HbA1C in the first trimester is associated with a higher risk of transfer to the neonatal intensive care unit and prematurity, even if glycemic control is corrected before the third trimester. In case of late imbalance, the HbA1c level is a marker of the risk of LGA. These results confirm the need to obtain a strict glycemic balance during the whole pregnancy but also the importance of pre-conceptional preparation.

Key Words: Type 2 diabetes, pregnancy, metabolic balance, HbA1C, maternal and fetal adverse pregnancy outcomes.

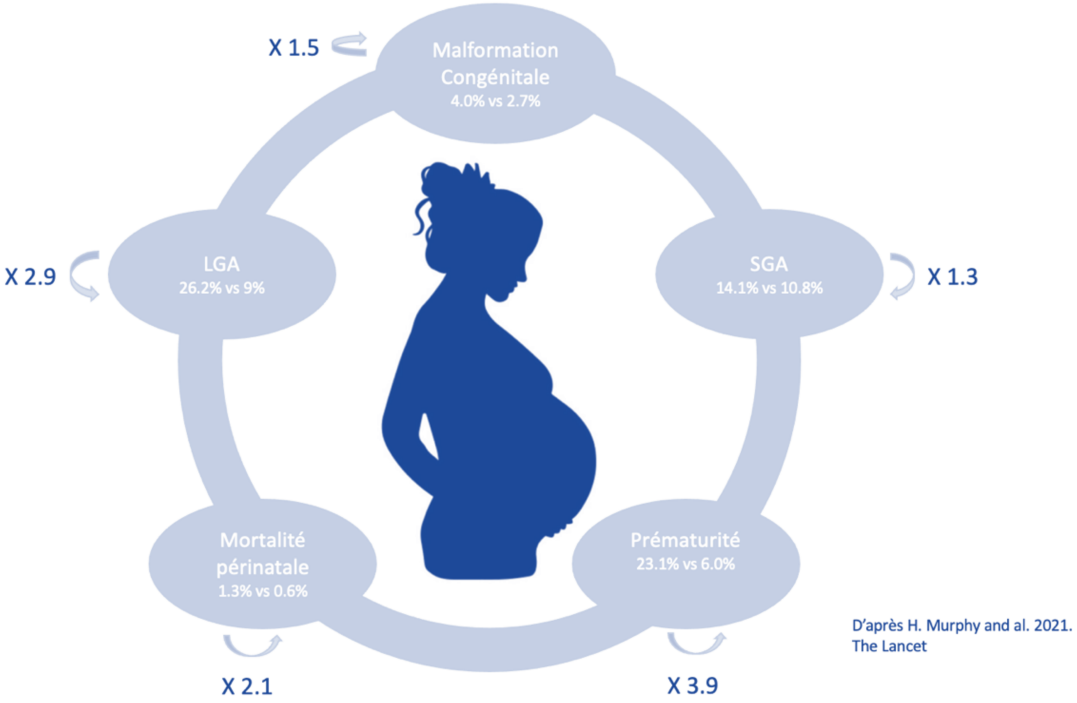
II- INTRODUCTION :

1/ Diabète de type 2 au cours de la grossesse :

Les grossesses compliquées par un diabète préexistant à la grossesse sont de plus en plus fréquentes, et représentent environ 1 grossesse sur 10 chez les femmes des 30 ans et plus (1–4). La fréquence des grossesses compliquées d'un diabète de type 2 (DT2) a augmenté de 90 à 110% en Europe en raison de la pandémie d'obésité, qui touche des adultes de plus en plus jeunes (5). De plus, ces grossesses surviennent chez des patientes de plus en plus âgées, plus souvent en situation d'obésité, issues de milieux sociaux plus précaires que dans la population générale ou que dans le cas du diabète de type 1 (4,6–11). Il est à présent reconnu que l'équilibre glycémique de ces patientes est meilleur que celui des patientes diabétiques de type 1 (DT1), en particulier en péri-conceptionnel. Pour autant, les grossesses restent à haut risque de complications (4,8–10,12,13). En comparaison au DT1, il semble que les malformations congénitales et la mortalité périnatale soient retrouvées à des incidences équivalentes (4). Cependant, les risques de prématurité, LGA (Large for Gestational Age), SGA (Small for Gestational Age), admission du nouveau-né en réanimation, ou césarienne sont majorés en comparaison à la population générale. Cependant, ils restent moins important que dans le cadre du DT1 (4,10,14–16). Récemment, Helen Murphy & al., ont montré sur une cohorte nationale anglaise de 5 ans, concernant 8685 grossesses DT2, que (4,17) :

- 26.2% présentent un LGA soit 2.9 X plus que dans la population non diabétique,
- 14.1% présentent un SGA soit 1.3 X plus que dans la population non diabétique,

- 23.1 % ont un enfant en condition de prématurité < 37 SA soit 3.9 X plus que dans la population non diabétique,
- 4.0 % présentent une malformation congénitale soit 2.7 X plus que dans la population non diabétique,
- 1.3% des enfants sont mort-nés soit 2.1 X plus que dans la population non diabétique,



Ces résultats montrent donc sans ambiguïté que les grossesses marquées par un diabète pregestationnel sont **associées à un excès significatif de morbi-mortalité materno-fœtale.**

Ce sur-risque de morbi-mortalité materno-foetale persiste alors même que ces grossesses sont suivies en centre expert, où les protocoles de prise en charge sont ceux préconisés par les sociétés savantes telles que l'ADA (American Diabetes Association), ou la SFD (Société Francophone de Diabétologie) qui définissent des objectifs

glycémiques plus strict au cours de la grossesse. Les recommandations actuelles préconisent une planification des grossesses chez les patientes diabétiques avec la nécessaire obtention au préalable d'une HbA1C < 6.5% en pré-conceptionnel et au 1er trimestre, tout en limitant le risque hypoglycémique, et < à 6.0% le reste de la grossesse (18). Pour se faire, les praticiens disposent de plusieurs outils tels que l'optimisation des aspects nutritionnels, l'activité physique, le recours à l'insulinothérapie selon un schéma multi-injection ou au besoin l'instauration d'une insulinothérapie par pompe sous cutanée. L'obtention de ces objectifs permet la réduction des complications maternelles et fœtales (19–22), avec comme souhait de s'approcher d'un risque de morbidité identique à celui des femmes non diabétiques. Force est de constater que malgré l'optimisation des prises en charge, l'objectif n'est pas atteint (21,23–25).

Outre l'équilibre glycémique, d'autres facteurs interviennent probablement dans la survenue de ces complications : on peut citer la variabilité glycémique, l'insulinorésistance médiée par le surpoids, l'obésité pré-gestationnelle (26,27), la prise excessive de poids au cours de la grossesse (7,12,28–31) et plus récemment, certains auteurs ont évoqué le possible impact des dyslipidémies (12,27,32–36).

2/ HbA1c:

- Généralités :

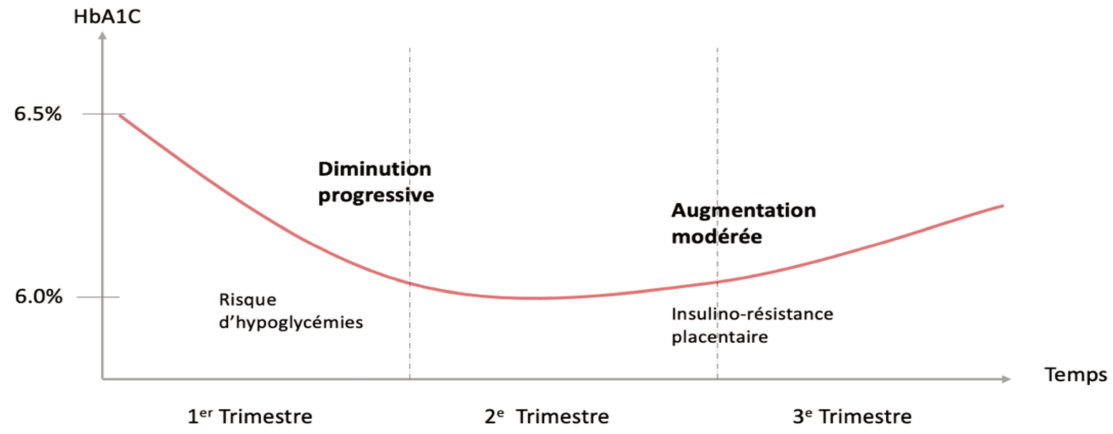
L'hémoglobine glyquée est un marqueur de routine, peu coûteux, reproductible, évalué sur un prélèvement sanguin veineux. Ce marqueur est le produit de la glycation de l'hémoglobine lorsque les hématies sont exposées au glucose sanguin. La durée de vie des hématies étant de 120 jours, l'HbA1C reflète l'équilibre glycémique à moyen terme sur les 3 derniers mois et est déterminée à 50 % par l'environnement glycémique

des 30 derniers jours. Ce marqueur est un marqueur de référence de suivi des patients diabétiques et un marqueur de risque de complications. Il faut cependant garder en mémoire que son dosage peut être biaisé par les facteurs influençant la durée de vie des hématies (splénomégalie, splénectomie, anémie, carences martiales, en B9, en B12, …). L'interprétation de l'HbA1C est alors difficile et il peut convenir d'utiliser d'autre dosage tel que la fructosamine plasmatique, ou d'utiliser les auto-surveillances glycémiques capillaires ou les glycémies veineuses à différents moment de la journée (37–39).

- HbA1c au cours de la grossesse :

Au cours de la grossesse,

- L'HbA1C est plus basse au cours du premier trimestre. Cela est lié à la survenue plus fréquente d'hypoglycémies et à un renouvellement plus rapide de la masse érythrocytaire, les érythrocytes sont alors moins soumis à la glycation,
- Son taux est plus faible au 2ème trimestre, pour les mêmes raisons suscitées,
- Une élévation du taux d'HbA1c est retrouvée au 3ème trimestre, devant une diminution de l'érythropoïèse mais aussi en lien avec les glycémies post-prandiales du 3ème trimestre qui sont, en général, plus élevées.



Évolution de l'HbA1C au cours de la grossesse :

3/ Diabète de type 2 et HbA1c au cours de la grossesse :

Les recommandations actuelles de prise en charge d'une grossesse compliquée d'un DT2 prégestationnel, sur lesquelles se basent nos pratiques actuelles, sont issues de la SFD et des recommandations de l'ADA et sont résumées ci-dessous :

- Programmation de la grossesse avec préparation multidisciplinaire en pré-conceptionnel et éducation thérapeutique de la patiente quant aux objectifs glycémiques, à l'intérêt de la perte de poids si surpoids/obésité, arrêt ou relais des traitements contre-indiqués au cours de la grossesse.
- Dès le diagnostic de grossesse, initiation d'un suivi dans un centre spécialisé dans la prise en charge du diabète au cours de la grossesse.
- Objectifs glycémiques :
    - Glycémie à jeun comprise entre 0.70-0.95 g/L (3.84-5.23 mmol/L)
    - Glycémies H1 post prandial 1.00 - 1.40 g/L (5.50-7.67 mmol/L)
    - Glycémie H2 post prandial 1. 00 - 1.20 g/L (5.50-6.60 mmol/L)
    - Autosurveillance glycémique 6 fois par jours

- Utilisation possible de capteur de mesure continue du glucose (type FreeStyle Libre – ABBOT Laboratories) au cours de la grossesse avec un intérêt prouvé sur l'équilibre glycémique chez les diabétiques de type 1. Les cibles sont alors de :
    - Temps dans la cible (0.63- 1.40 g/L) > 70%
    - Temps inférieur à la cible (<0.63 g/L) < 4%
    - Temps inférieur à la cible (<0.54 g/L) < 1%
    - Temps supérieur à la cible (>1.40 g/L) < 25% (18).

4/ Bibliographie :

Bibliographie récente concernant le lien entre l'HbA1c, le diabète de type 2 et les complications materno-fœtales au cours de la grossesse :

Article s'intéressant à l'HBA1C comme facteur prédictif	Effectif	Design	HbA1c	Résultats
"Impact of type 2 diabetes, obesity and glycaemic control on pregnancy outcomes" S. Abell & al, 2016 (40)	131 DT2	Rétrospectif Multicentrique	Moyenne tout au long de la grossesse	Augmentation de 1% HbA1C associée à : o augmentation de macrosomie (OR : 1.56), o augmentation des hypoglycémies néonatales (OR 1.46), o augmentation de mortalité périnatale (OR 2.80), o augmentation du LGA (OR 1.56),
« Type 2 diabetes mellitus in pregnancy: The impact of maternal weight and early glycaemic control on outcomes" M. Bashir & al, 2018 (7)	419 DT2	Rétrospectif Monocentrique	T1 et T3	HBA1C T1 associée à : o LGA (OR 1.17), o Préeclampsie (OR 1.26), o NICU (OR 1.32), HBA1C T3 associée à : o LGA (OR 1.53), o Césarienne (OR 1.37),
"The use of longitudinal hemoglobin A1c values to predict adverse obstetric and neonatal outcomes in pregnancies complicated by pregestational diabetes" M. Finneran & al, 2019 (41)	341 DT2	Rétrospectif Monocentrique	HbA1C < 20SA et > 20SA	Contrôle glycémique optimal = groupe référence, Groupe équilibre en amélioration (<20SA > 6.5% et > 20SA <6.5%) associé à NICU avec OR 3.7 Groupe mauvais équilibre (hbA1c <20SA et > 20SA > 6.5%) associé à o dystocie des épaules (OR 6.8), o prématurité (OR 3.9),

				○ NICU (OR 2.8), ○ LGA (OR 2.5), ○ Prééclampsie (OR 2.4),
"Congenital malformation and hemoglobin A1c in the first trimester among Japanese women with pregestational diabetes" K. Nakanishi & al, 2021 (42)	156 DT2	Rétrospectif Monocentrique	Cible d'HbA1C lors du 1er trimestre < 6.5% pour limiter les malformations congénitales.	
"Obstetric and perinatal outcomes in pregnancies complicated by Type 1 and Type 2 diabetes: influences of glycaemic control, obesity and social disadvantage" H. Murphy & al, 2011 (16)	274 DT2	Cohorte prospective Multicentrique	T3	L'HbA1C T3 est un facteur prédictif de LGA (OR 1.35)chez les patientes avec un diabète prégestationnel
"The effects of first-trimester diabetes control on the incidence of macrosomia" E. Rey & al, 1999 (43)	120 DT2	Rétrospectif Monocentrique	T1	Augmentation de la macrosomie (OR à 4.8)
"Can hemoglobin A1c in early pregnancy predict adverse pregnancy outcomes in diabetic patients?" R. Starikov & al, 2014 (44)	330 (DT1 +DT2)	Rétrospectif Monocentrique	T1	HbA1C > 8.0% : augmentation du risque de dystocie et de LGA
Article s'intéressant aux complications materno-fœtales en comparaison à la population générale	**Effectif**	**Design**		**Résultats**
"Impact of type 2 diabetes, obesity and glycaemic control on pregnancy outcomes" S. Abell & al, 2016 (40)	138 DT2	Rétrospectif Multicentrique		Augmentation : ○ LGA (OR 2.13), ○ Dystocie des épaules(OR 2.74), ○ Césarienne (OR 2.10), ○ Prééclampsie (OR 2.75),
« Type 2 diabetes mellitus in pregnancy: The impact of maternal weight and early glycaemic control on outcomes" M. Bashir & al, 2018 (7)	419 DT2	Rétrospectif Monocentrique		DT2 associé à ○ Prématurité (OR 1.74), ○ Préeclampsie (OR 1.69), ○ Césarienne (OR 1.52), ○ LGA (OR 1.99), ○ NICU (OR 1.86), ○ Dystocie des épaules(OR 1.04),
"Poor pregnancy outcome in women with type 2 diabetes" T. Clausen & al , 2005 (10)	213 DT2	Rétrospectif Monocentrique		DT2 associé à plus de prééclampsie, césarienne, dystocie des épaules, prématurité, LGA, hypoglycémies néonatales, NICU, hémorragie de la délivrance.
"A Population-Based Study of Diabetes During Pregnancy in Spain (2009-2015): Trends in Incidence, Obstetric Interventions, and Pregnancy Outcomes" A.López-de-Andrés & al, 2020 (13)	4391 DT2	Rétrospectif Multicentrique		DT2 associé à plus de : ○ prééclampsie, ○ césarienne (OR 1.75), ○ complications maternelles (OR 1.25), ○ LGA (OR5.55)
Articles récents s'intéressant aux différences de complications materno-fœtales entre DT1 et DT2	**Effectif**	**Design**		**Résultats**
"Temporal changes in characteristics and outcomes among pregnant women with pre-gestational diabetes" J. Alessi & al , 2018 (9)	135 DT2	Rétrospectif Monocentrique		Pas de différence en dehors d'une diminution du NICU chez DT2
"Fetal overgrowth in women with type 1 and type 2 diabetes mellitus"	87 DT2	Rétrospectif Monocentrique		DT2 associé à :

L. Ladfors & al, 2017 (12)			○ moins de prématurité, ○ moins de LGA, ○ moins de macrosomie, ○ moins d'hypoglycémies néo-natales,
"Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study" H. Murphy & al, 2021(4)	8685 DT2	Rétrospectif Multicentrique	DT2 associé à : ○ moins de prématurité, ○ moins de LGA, ○ moins de NICU, ○ plus de mortalité périnatale
"Risk factors for pregnancy outcomes in Type 1 and Type 2 diabetes" J. Seah & al, 2021 (11)	106 DT2	Rétrospectif Monocentrique	DT2 associé à : ○ moins de LGA avec OR DT1 versus DT2 à 3.2
"Obstetric and perinatal outcomes in pregnancies complicated by Type 1 and Type 2 diabetes: influences of glycaemic control, obesity and social disadvantage" H. Murphy & al, 2011 (16)	274 DT2	Prospectif Multicentrique	DT2 associé à : ○ moins de LGA, ○ moins de prématurité, ○ moins de NICU
Articles s'intéressant à l'impact de la prise en charge sur les issues de grossesse	**Effectif**	**Design**	**Résultats**
"The prevalence of congenital malformations is still higher in pregnant women with pregestational diabetes despite near-normal HbA1c: a literature review" N. Eriksen & al, 2019 (24)	2334 DT2	Revue de littérature	Le RR de malformation congénitale reste supérieur avec OR 2.2 malgré HbA1C pré-conceptionnelle < 7.0%
"Association of Improved Periconception Hemoglobin A1c With Pregnancy Outcomes in Women With Diabetes" A.Davidson & al, 2020 (23)	3459 DT1 + DT2	Rétrospectif Multicentrique	Pour chaque diminution de 0.5% HbA1C : ○ OR de 0.94 pour la malformation congénitale, ○ OR 0.89 pour la prématurité, ○ OR 0.90 pour la mortalité périnatale
"Type-2 diabetes mellitus: does prenatal care affect outcomes?" A.Allen & al, 2018 (19)	38324 DT2	Rétrospectif Multicentrique	Comparée au patientes prise en charge au T1 la prise en charge des patientes au T3 est associé à, ○ OR de 11.37 pour la mort fœtale in utero ○ OR de 1.55 pour la prématurité
"Association of change in haemoglobin A1c with adverse perinatal outcomes in women with pregestational diabetes" M. Kiefer & al, 2022 (20)	347 DT1 + DT2	Rétrospectif Monocentrique	La diminution de 0.5% HbA1C entre le début et la fin de grossesse permet : ○ réduction de 12% du LGA, ○ de 7% de la prématurité, ○ de 5% du NICU

5/ Objectif et Design :

En dépit de l'optimisation glycémique facilitée par l'avènement des nouvelles technologies, les grossesses compliquées d'un diabète de type 2 préexistant à la grossesse restent des grossesses à risque de complications maternelles et fœtales, en comparaison à des sujets non diabétiques. L'HbA1C est le gold standard du suivi à moyen terme des patient diabétiques. Il est également utilisé au cours de la grossesse, période pendant laquelle des seuils spécifiques sont recommandés afin de limiter les issues défavorables de grossesse.

Ce dosage pourrait permettre de prédire l'apparition de certaines complications, au-delà de son intérêt dans le contrôle de l'équilibre glycémique. La plupart des études s'intéressent uniquement à l'équilibre glycémique sur l'ensemble de la grossesse sans distinguer l'impact de la temporalité du déséquilibre glycémique sur les dites complications.

Le but de cette étude est de **déterminer si l'HbA1C permet de prédire la survenue d'issues défavorables au cours des grossesses chez les femmes diabétiques de type 2,** en s'intéressant en particulier au déséquilibre glycémique lors du 1er et 3ème trimestre.

Pour cela, nous avons recueilli et analysé de manière rétrospective l'ensemble des grossesses de femmes diabétique de type 2, ayant donné naissance à un enfant unique vivant, entre 1997 et 2021 au CHU de Lille. Nous avons exclu les patientes diabétiques de type 1, les diabètes gestationnels, les autres diabètes, les accouchements dans un autre centre, et les grossesses gémellaires.

Les données démographiques, les antécédents obstétricaux, les données concernant le diabète et ses complications, les données obstétricales, néonatales et maternelles ont été recueillies à partir du dossier médical. Toutes les patientes ont bénéficié du même suivi diabétologique et obstétrical au sein de notre centre qui est une maternité de niveau III. Les prises en charges diabétologiques suivaient les recommandations de la SFD et de l'ADA, les prises en charges obstétricales suivaient les recommandations du CNGOF.

Les résultats vous sont présentés dans l'articles ci-dessous.

III- ARTICLE:

Association between HbA1c levels on adverse pregnancy outcomes during type 2 diabetes mellitus pregnancy

Abbreviations:

ADA: American Diabetes Association
BMI: Body Mass Index
CHRU: Centre Hospitalier Régional Universitaire
CI : Confidence Interval
CGMS: Continuous Glucose Monitoning Sensor
CNGOF: Collège National des Gynécologues et Obstétriciens Francais
CSII: Continuous Subcutaneous Insulin Infusion
DT1/T1D: Type 1 Diabetes
DT2/T2D: Type 2 Diabetes
HbA1C: Hemoglobin Glycated
HTA: Hypertension
NICU: Neonatal Intensive Care Unit
IQR: Interquartile Range
IUFD: Intra Uterine Fetal Death
LGA: Large for Gestational Age
OR: Odds Ratio
RR: Relative Risk
SD: Standard Deviation
SFD: Societé Francophone de Diabétologie
SGA: Small for Gestational Age
WHO: World Health Organisation

INTRODUCTION:

In 15 years, the incidence of pregnancies complicated by diabetes increased two times. Most of it concern gestational diabetes. However, the maternal fetal risks in term of morbidity and mortality are predominant in preexisting diabetes at pregnancy (13). As the obesity continues to rise, type 2 diabetes in young women in age of childbearing increased of 90-110% (1–4). The most maternal and fetal adverse outcomes encountered are congenital malformations, prematurity, perinatal death, preeclampsia, macrosomia, large for gestational age (LGA), small for gestational age (SGA), neonatal intensive care unit admission, cesarean sections (4,10,14,16,32). Recently, H. Murphy & al. reported a national follow-up cohort regarding pregestational diabetes in pregnancy which described a quarter of LGA (26.2%), 14.1% were marked by SGA, another quarter of preterm newborns (23.1%), and 4.0% were diagnosed with congenital disease (4).

There are many recommendations to reduce the risk of adverse pregnancy outcomes. Their goal is to control and achieve blood glucose levels as close as possible to those observed in non-diabetic populations. HbA1C is the gold standard for glycemic control, and recommendations are for a goal of HbA1C < 6.5% in the preconception period and in early pregnancy, with as few hypoglycemic episodes as possible, and HbA1C < 6.0% in the second and third trimester of pregnancy (17). Despite the improvement in glycemic control with new technologies, adverse events still remain higher in pregnant women with type 2 diabetes compared with women without diabetes. In the literature, HbA1c levels are strongly associated with adverse maternal and fetal outcomes (4,15,16,22,36-43), but this impact appears to differ depending on the trimester of pregnancy studied (7,16,40,41,43,44).

The aim of our study was to evaluate the impact of 1st and 3rd trimester HbA1C on the main adverse outcomes in pregnancies complicated by type 2 diabetes followed in the same tertiary obstetric care center and by the same multidisciplinary professionals. We also evaluate the impact of the timing of metabolic imbalance by conducting subgroups analyses. We defined 4 groups of metabolic control: Group I was 1st trimester Hba1C < 6.5% and 3rd trimester HbA1C < 6.0%, group II was 1st trimester Hba1C > 6.5% and 3rd trimester HbA1C > 6.0%, group III was 1st trimester Hba1C > 6.5% and 3rd trimester HbA1C < 6.0% and group IV 1st trimester Hba1C < 6.5% and 3rd trimester HbA1C > 6.0%.

RESEARCH DESIGN:

We conducted a single center, retrospective, observational cohort study at the University Hospital of Lille in France. This study was based on paper and electronic medical records. Under French law, care-related data may be used for research purposes unless the patient opposes such use. Data were analyzed anonymously, and our database was declared to the French Committee for computerized data. We included all women with pregestational type 2 diabetes mellitus who gave birth to a single alive newborn in our center between 1997 and 2021. Women were excluded if they had type 1 diabetes mellitus, gestational diabetes, syndromic diabetes, secondary diabetes, or if they were patients under the age of 18. Twin/multiple pregnancies, miscarriages, intra uterine fetal death were excluded.

Data collection:

Maternal demographics data, diabetes complications and duration, obstetrical history, fetal and maternal adverse pregnancy outcomes were collected. Patients performed self-monitoring of glucose levels by capillary blood glucose monitoring or by continuous measurement of interstitial glucose. Diabetes follow up consisted in regular HbA1c assay, patients were contacted by a specialized nurses twice a week to assess glucose control and adjust treatment if needed. Patients were treated with diet alone, multi-daily insulin injection or with subcutaneous insulin infusion. Glycemic targets were < 0.95 mg/dl before meals and < 1.20 mg/dl 2h after meals. 1st trimester Hba1c target was < 6.5 % and 3rd trimester HbA1c target was < 6.0%. Obstetrical follow up was performed monthly. Obstetrical and diabetological follow up were consistent to the French national guidelines (French Society of Diabetes SFD and French National College of Obstetricians and Gynecologist CNGOF).

Outcomes definitions:

Concerning maternal democraphic data, age, height, body weight were recorded and body mass index (BMI) was defined. Hypertension before pregnancy (defined as blood pressure > 140/90 mmHg or use of antihypertensive treatment before pregnancy), weight gain at 1st, 2nd, 3rd trimester, total weight gain, and smoking status were equally collected.

Diabetes history was assessed: the duration of diabetes, the prepregnancy type of treatment (diet alone, oral treatment, basal insulin injection, multi-injection of insulin, SCII), type of treatment during pregnancy (diet alone, multi-daily injection of insulin, SCII), history of vascular complications of diabetes (retinopathy, nephropathy,

neuropathy,) appearance/aggravation of vascular complication (appearance or deterioration of retinopathy, nephropathy). We also collected pre-pregnancy HbA1C, 1st Trimester HbA1C, 2nd trimester HbA1C, 3rd trimester HbA1C. We collected the type of self-monitoring of glucose levels (capillary or continuous interstitial measurement) and the type of contact used with the patient (2/week call, 2/week electronical contact by MyDiabby or by LibreView).

Obstetrical history was assessed: gravidity, parity, history of miscarriage (defined as loss of pregnancy before 22 amenorrhea weeks), history of intra uterine death (define as loss of pregnancy after 22 amenorrhea weeks), history of macrosomia or preeclampsia.

Concerning maternal adverse pregnancy outcomes, we counted episode of gravidic hypertension (defined as apparition of blood pressure > 140/90 mmHg after 20 amenorrhea weeks), and episode of preeclampsia (defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg and proteinuria > 300 mg/day after 20 amenorrhea weeks). Prematurity was defined as birth before 37 amenorrhea weeks. Equally, delivery (cesarean section of vaginal delivery), shoulder dystocia and delivery hemorrhage (defined as blood loss > 500 ml in the 24h following the delivery) were counted. Admission of the mother in intensive care unit was collected.

Concerning neonatal adverse pregnancy outcomes, term, weight of birth were defined. Large for Gestational Age (LGA), defined as weight > 90th percentile, was calculated using the AUDIPOG formula. Small for Gestational Age (SGA), defined as weight < 10th percentile, was calculated using AUDIPOG formula. Macrosomia was defined by

a weight of birth > 4000 grams. Congenital malformations were recorded and admission in neonatal intensive care unit was collected.

The aim of our study was to evaluate the impact of 1st and 3rd trimester HbA1C imbalance on principal maternal and fetal adverse pregnancy outcomes in our center : LGA, SGA, prematurity, malformation, preeclampsia, transfer to NICU. We also performed a subgroup analysis comparing LGA, SGA, prematurity, preeclampsia, NICU transfer according to metabolic balance levels. Four groups were defined as follows: Group I had optimal balance throughout pregnancy (1st trimester HbA1c <6.5% and 3rd trimester HbA1C <6.0%), Group II had glycemic imbalance throughout pregnancy (1st trimester HbA1c >6.5% and 3rd trimester HbA1C >6. 0%), group III had early imbalance but progressive correction during pregnancy (1st trimester HbA1c >6.5% and 3rd trimester HbA1C <6.0%); and group IV had late third trimester glycemic imbalance (1st trimester HbA1c <6.5% and 3rd trimester HbA1C >6.0%).

Statistical Analysis:

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. We assessed the association of HbA1c with pregnancy outcomes (all binary) using logistic regression models with and without adjustment on predefined risk factors (year of delivery – per group of 5 years, for compliance with weight gain recommendations according to pre gestational BMI). We firstly studied HbA1c in the first trimester, and then in the third

trimester, considering HbA1c as continuous variable, except when log linearity was not assessed. Log-linearity assumption for continuous features was examined using restricted cubic spline functions. If log linearity was not assessed, we binarized the Hba1c by taking the threshold of 6.5 in the first trimester and the threshold of 6 in the second trimester. The results were expressed in odds ratios (OR) and their 95% confidence intervals (CI) calculated per 1% increase in HbA1c if continuous or below the threshold if binary. Secondly, we examined the association by considering HbA1c as a 4-level categorical variable using pre-specified HbA1c classes: <6.5% in the first trimester and <6.0% in the third trimester, ≥6.5% in the first trimester and ≥6.0% in the third trimester, ≥6.5% in the first trimester and <6.0% in the third trimester, and <6.5% in the first trimester and ≥6.0% in the third trimester. We assessed the association of the 4-level HbA1c with pregnancy outcomes using logistic regression models before and after adjustment on predefined risk factors (year of delivery – per group of 5 years, for compliance with weight gain recommendations according to pre gestational BMI). The results were expressed in odds ratios (OR) and their 95% confidence intervals (CI) using HbA1c <6.5% in the first trimester and <6.0% in the third trimester as reference group. To avoid bias, missing data were handled by multiple imputation(45,46)[i], under missing at random assumption, by using regression switching approach (multivariate imputation by chained equations with m=10 imputations) with predictive mean matching method for continuous variables, logistic regression models (binomial, ordinal or multinomial) for categorical variables. The results of each imputed dataset were combined using Rubin's rules[ii]. Statistical testing was done at the 2-tailed level of 0.05.

RESULTS:

Demographic characteristics of type 2 diabetic population:

In this single-center observational study, 1651 patients were followed between 1997 and 2021 at the Lille University Hospital, by the Diabetes and Pregnancy unit. After exclusion of patients with type 1 diabetes, gestational diabetes, secondary diabetes or syndromic diabetes, 689 women were eligible. Secondly, 60 were excluded for miscarriage, 14 for FDIU, 16 for multiple pregnancies. 1 patient was excluded for hemopathy (HbA1C uninterpretable). 15 patients were lost to follow-up. Finally, 583 pregnancies in type 2 diabetic patients with live births were included (Figure 1).

Baseline maternal characteristics:

The clinical characteristics are presented in Table 1. The mean age of the patients was 33.9 years (± 5.4). The mean preconception BMI was 34.9 kg/m2 (± 7.10), the mean total weight gain during pregnancy was 8.0kg (IQR 3.0-12.0). The duration of diabetes was 2.0 years (IQR 0.0-5.0). Prior to pregnancy, the patients were mainly untreated for diabetes (55.3%). Self-monitoring of blood glucose was mainly done by capillary (94.7%) and contact with the structure was done in most cases by telephone. 88.8% of the patients were treated with basal bolus insulin therapy during pregnancy, 6.2% with insulin pumps and 5.0% with RHD alone. Only 39 (6.7%) had diabetic vascular complications: diabetic nephropathy was present in 22 women (3.8%), diabetic retinopathy in 17 women (2.3%), and pregravid hypertension in 93 women (16.0%). Most of the patients were multiparous (82.7%), 25% had an history of macrosomic birth, 42% had a history of gestational diabetes. 25% had a history of a miscarriage and 8.9% had a history of fetal death in utero.

Metabolic balance during pregnancy:

According to American Diabetes Association recommendation, women had to target an HbA1c ≤ 6.5 % at first trimester, and ≤ 6 % at third trimester. The mean HbA1c level during pregnancy was 6.3% (45 mmol/mol) (± 0.70). Prepregnancy HbA1c was 7.0% (53 mmol/mol) (± 1.4). As expected, HbA1c values decreased during pregnancy: median HbA1c in the first month was 6.7% (50 mmol/mol) (± 1.3)), 6.3% (45 mmol/mol) (± 0.99) in the first trimester, 5.9% (41 mmol/mol) (± 0.8) in the 2nd trimester, and 5.9% (41 mmol/mol) (± 0.75) in the third trimester (Figure 2). 41.6% (n=242) of patients had "optimal" metabolic control throughout pregnancy, 24.2% (n=141) had "poor" control throughout pregnancy 11.3% (n=66) had early imbalance control and 22.9% (n=134) had late metabolic imbalance during pregnancy (Table 2).

Adverse maternal-fetal outcomes during pregnancies in T2D:

Adverse maternal-fetal outcomes are presented in Table 3. Concerning maternal adverse outcome, 12.0% (n=70) developed gestational hypertension, 7.9% (n=46) preeclampsia and 49.4% (n=287) of deliveries were by cesarean section. 18.1% (n=105) of the patients had a delivery hemorrhage and 1.2% (n=7) were admitted to intensive care. Concerning the newborn, the median term was 38.1 SA (38SA+0d) with a prematurity rate was 15.6% (n=91). Shoulder dystocia complicated 1.4% of births (n=8). 5.3% of newborns had a malformation (n=31). 12.1% (n=71) of newborns were transferred to neonatal intensive care. The average weight of newborns was 3 329 g (median weight of newborns was 3 360 (IQR 3,020-3,760). 29.2% (n=170) of the children were LGA, 7.9% (n=46) were small for gestational age. Among the 31 neonatal birth defects, 9 (29%) were congenital heart defects, 6 (19%) were renal birth defects, 5 (16%) were digestive and 5 (16%) were polymalformations. 2 (7%) were facial

malformations, 2 (7%) were central nervous system malformations. Only 1 (3%) was a genital malformation and another 1 (3%) was an osteological system malformation (Figure 3).

HbA1c and pregnancy outcomes:

Higher HbA1c during the first trimester was associated with LGA (OR 1.33; 95% CI 1.09-1.62 per 0.1% increase; P =0.004), prematurity (OR 1.39; 95% CI 1.11-1.75 per 0.1% increase; P = 0.004), cesarean (OR 1.66; 95% CI 1.11-2.48 per 0.1% increase; P = 0.014) and NICU admission (1.75; 95% CI 1.33-2.29 per 0.1% increase; P <0.001) (Fig. 2). Higher HbA1c during the third trimester was also associated with the LGA (OR 2.67; 95% CI 1.75-4.07 per 0.1% increase; P < 0.001), cesarean (OR 1.30; 95% CI 1.02-1.66 per 0.1% increase; P = 0.031) and NICU admission (OR 1.43; 95% CI 1.02-2.01 per 0.1% increase; P = 0.038). Preeclampsia and SGA were not associated with first and third trimester HbA1C (Figure 4).

Four glycemic control subgroups, defined by HbA1c levels in the first and third trimesters, were created in order to define the period during which HbA1c was a better predictor of maternal–fetal morbidity: group I was optimal balance throughout pregnancy and included 41.5% (n=242) of the cohort and was considered the reference group; group II had had glycemic imbalance throughout pregnancy, making up 24.2% (n=141) of the population; group III had early imbalance but progressive correction during pregnancy and represented 11.3% (n=66) of the population; and group IV had a late glycemic imbalance in the third trimester, representing 23.0% (n=134) of the population. Associations of HbA1c and most individual adverse events, according to these glycemic control levels, are presented in Table 4. Using patients from group I as

reference, group II was associated with an increased rate of the LGA (OR 2.94 ; 95% CI 1.75-4.96), an increased rate of prematurity (OR 2.25 ; 95% CI 1.25-4.19), cesarean (OR 1.86; 95% CI 1.18-2.96), neonatal malformation (OR 4.91 ; 95% CI 1.62-14.90) and NICU admission (OR 3.41 ; 95% CI 1.63-7.14). Patients from group IV were also associated with an increased rate of the LGA (OR 2.97; 95% CI 1.68-5.27), using patients from group I as reference. Patients from group III were associated with an increased rate of the NICU admission (OR 4.59; 95% CI 1.73-12.15). Analyses on neonatal malformation was performed for group II, using group I as reference. Group II was associated with an increased rate of malformation (OR 4.91; 95% CI (1.62 to 14.90). Due to the low number of events, group III and IV could not be analyzed. Preeclampsia is not statistically associated with glycemic control levels. Analyses in subgroups could not be conducted for SGA and shoulder dystocia because of the insufficient number of events. In summary, LGA is associated with late glycemic imbalance: group II (poor glycemic balance throughout pregnancy) and group IV (late glycemic imbalance). NCIU admissions is associated with early glycemic imbalance group III (early glycemic imbalance) and group II (poor glycemic balance throughout pregnancy).

Focus on NCIU Admissions:

Indications of NICU transfer are presented in figure 5. 71 newborns were admitted to NICU during our study: 15 (21%) for neonatal malformation, 14 (20%) for respiratory distress, 5 (7%) for infection, 15 (21%) for prematurity >32 weeks of amenorrhea, 11 (16%) for great prematurity 28-32 weeks of amenorrhea, 4 (6%) for extreme prematurity < 28 weeks of amenorrhea, 3 (4%) for circulatory distress, 2 (3%) for neonatal hypoglycemia, 1 (1%) for convulsion. In the group composed by patients with glycemic

balance throughout pregnancy, the major causes of NICU admission were a mild prematurity and fetal respiratory distress. Among patient with glycemic imbalance throughout pregnancy, main causes of NICU admission were great and mild prematurity, neonatal malformations, fetal respiratory distress and circulatory distress. In patients with early glycemic imbalance, NICU admission was justified by mild and great prematurity, neonatal malformations, neonatal hypoglycemia. Newborns of patients with late glycemic imbalance were admitted to NICU for great prematurity, fetal respiratory distress and neonatal malformations (data not shown).

DISCUSSION:

The objective of our study was to evaluate the impact of glycemic imbalance, estimated by 1st and/or 3rd trimester HbA1C, on major maternal and fetal complications during type 2 diabetic pregnancies. Through our large monocentric and retrospective cohort of type 2 diabetic women, we demonstrate the existence of an association between 1st and 3rd trimester HbA1c with maternal and fetal complications. Beyond that, we also highlighted that, for each augmentation of 1st trimester HbA1c level, the risk for some adverse outcomes such as neonatal intensive care unit admission increases, while 3rd trimester HbA1c level could be associated with the risk of large for gestational age. In the era of continuous glucose measurement, HbA1C thus remains a routinely used biomarker that seems to be associated with adverse maternal and fetal outcomes in these pregnancies marked by pregestational diabetes.

Our cohort of pregnant women with type 2 diabetes was similar to those previously described in the literature regarding age, duration of diabetes, low proportion of diabetic complications, multiparity, history of hypertension, history of gestational diabetes

[1-6]. However, the mean BMI was 34.9 kg/m2, which was higher than that observed in the Murphy & al.'s and Abell & al.'s cohort (mean BMI of 32 kg/M2) [4-6] but was consistent with the mean BMI of the Bashir's study [4]. Note that our center is located in the North of France, a department marked by an excess of overweight and obesity [5] . Moreover, weight gain during pregnancy was in line with the recommendations established for the general population, but was nevertheless higher than the recommended weight gain in the obese population during pregnancy [7].

Regarding neonatal complications, 15% prematurity, 7.9% pre-eclampsia, 29% LGA, 7.9% SGA, 49% caesarean sections were counted, which is consistent with the literature [1-3,6,8]. The rate of congenital malformations was similar to that observed by Inkster et al, in a review of the literature [9]. In addition, the NICU admission rate of 12.7% in our cohort is consistent with that observed in 2021 by Murphy & al in a retrospective cohort of pregnant women with pre-existing type 1 and type 2 diabetes [5]. Shoulder dystocia had a low frequency of 1.4% in our study while it was observed in 7.0% of newborns in a retrospective cohort study of 213 T2 diabetic women who delivered at the University of Rochester Strong Memorial Hospital in New York published by Knight et Al 2012 [10]. Probably, there is a center effect since our maternity hospital is a tertiary care center.

In our study, the mean HbA1C during pregnancy was correct at 6.0% and, consistent with the literature, we observed an improvement in HbA1C during pregnancy from 7.0% before conception to 6.3% in the first trimester and to 5.0% in the second and third trimesters. However, it is interesting to note that 60% of patients in our study had glycemic imbalance during pregnancy: 24% had imbalance throughout pregnancy and

22.9% had initial control and late imbalance, demonstrating a failure of preconception management strategies in type 2 diabetes. Our results highlight an association between HbA1C during pregnancy and cesarean section, LGA, prematurity, neonatal birth defects, and NICU admission. In our study, preeclampsia was not associated with HbA1C in pregnancy, unlike Bashir et al [4]. However, Lemaitre et al in a retrospective study among pregnant women with type 1 diabetes in our center, HbA1C was not associated with preeclampsia either [11]. Our percentage of preeclampsia is also similar to other tertiary care centers.

It seems early glycemic imbalance objectified by Hb1AC in 1st trimester > 6.5% could predict NCIU admission and prematurity. This may be explained by the increased number of neonatal malformations induced by a pre-conceptional and early glycemic imbalance (7,47)**.** This is supported by the larger proportion of neonatal birth defects found in the newborn admission in NICU in groups II (glycemic imbalance throughout pregnancy) and III (early glycemic imbalance)(data not shown). We also found a larger proportion great and extreme prematurity and of fetal respiratory distress in those groups. In Sweden, a retrospective cohort, also found an association with maternal overweight or obesity and extremely preterm deliveries (48). However, in the literature, it is the closest to the delivery hbA1C that was associated with extreme preterm delivery in type 1 diabetes (49,50). In a retrospective cohort study of 6774 women in Shangai, respiratory distress syndrome was 4.32 times more frequent in women with early HbA1c > 5.2% (51). Few data exist on NICU admissions of children born to mothers with diabetes. Sperling J. & al, report a study of 443 women with pre-existing diabetes and 499 with gestational diabetes. Newborns of women with pregestional diabetes, with poorer adherence to follow-up organized by the Diabetes in Pregnancy

Department, had higher rates of NICU admission or stillbirth (55 vs. 39%; p: 0.003). Multivariable logistic regression showed that the low-adherence group had a higher probability of NICU admission (adjusted odds ratio: 1.61 [1.03-2.5]; p: 0.035). In fact, those with poorer adherence had poorer glucose monitoring and more hospitalizations (52). Unfortunately, we do not have this data in our retrospective collection. A 2003 New Zealand study found a 40% transfer rate to the NICU for children born to T2D mothers. The reasons for admission were 42% prematurity, 58% hypoglycemia and 50% respiratory distress. These figures note an important pitfall of our work: lack of data on neonatal hypoglycemia (53).

We found that late glycemic imbalance (group II and IV) objectified by HbA1c > 6.0% in third trimester, is associated with LGA. This is inconsistent with data existent with the findings of Bashir and Al & Rey and al. (1st trimester HbA1c was associated with LGA), and Raychaudhuri & al. who find LGA was associated with glycemic imbalance prior to 20 weeks of amenorrhea in insulino-dependent diabetic patients (7,42,43). However, Murphy & al. in 2011 found that HbA1C in 3rd trimester was the main factor associated with LGA (16). Interestingly, we found that the leading causes of NICU admission of newborns in patient with late glycemic imbalance were congenital malformation and great prematurity (49,50). This may be in relation with the increased risk of congenital malformation observed in pregnancies complicated by GDM (54) and in pregnancies of Type 2 diabetic women with good early metabolic control (24,55). The mechanisms remains unclear: hypoxia, increased oxydative stress, apoptosis, epigenetic changes may be involved (55).

In patients with optimal glycemic control, the leading cause of NICU admission was prematurity >32 weeks' amenorrhea, which had a better prognosis. These results suggest that glycemic control improves pregnancy outcome, but is not sufficient in itself to reduce and eliminate the risk of adverse outcome (23). In our study, SGA was not associated with glycemic control, SGA was not increased if optimal glycemic control was achieved, showing the safety of achieving glycemic goals.

Our study has several strengths: the large number of type 2 diabetes women and the evaluation by the same multidisciplinary team, the low proportion of lost to follow up which gives our study a strong power. The consistency of our population with the population described in literature increase the external validity of our results even if our study is monocentric. We conducted multivariate analyses with pregestational BMI and gestational weight gain increasing the internal validity of our result. The exclusion of a patient with hemoglobinopathy increases the validity of our result. Our study is the first, at our knowledge, showing an association between HbA1C in early pregnancy and NCIU admissions in pregnancies of type 2 diabetic patients. However, the retrospective design, the long time period of inclusion are weaknesses of our study. First, we don’t know the hemoglobin and mean corpuscular volume (MCV) levels in our patients, so we were unable to account for the presence of hemoglobinopathy or iron deficiency and anemia, which can impact the accuracy of HbA1c assessment during pregnancy. Second, the lack of data regarding neonatal hypoglycemia is a major pitfall of this work. Thirdly, due to missing data, we had to imputate data, this could induce a lack of power in statistical analyses.

In conclusion, HbA1C is a valid, reproducible marker in routine practice for assessing glycemic control during pregnancy. HbA1C is associated with maternal and fetal complications such as prematurity, delayed weight-bearing, neonatal malformations, admission to NICU, caesarean sections, during the whole pregnancy. Interestingly, for every 0.1% increase in first-trimester HbA1C, the risk of NICU admission increases, possibly in relation to neonatal malformation. This risk persists despite correction of glycemic imbalance in the third trimester. Each increase in HbA1C in the third trimester increases the risk of LGA, even if glycemic control was ideal in early pregnancy. The improvement in glycemic control seems, however, to be insufficient for the risk of complications to be the same as in the non-diabetic population, suggesting the involvement of other metabolic mechanisms (glycemic variability, insulin resistance, BMI, inadequate gestational weight gain, toxic lipid profile) (27,34).

TABLE & FIGURES:

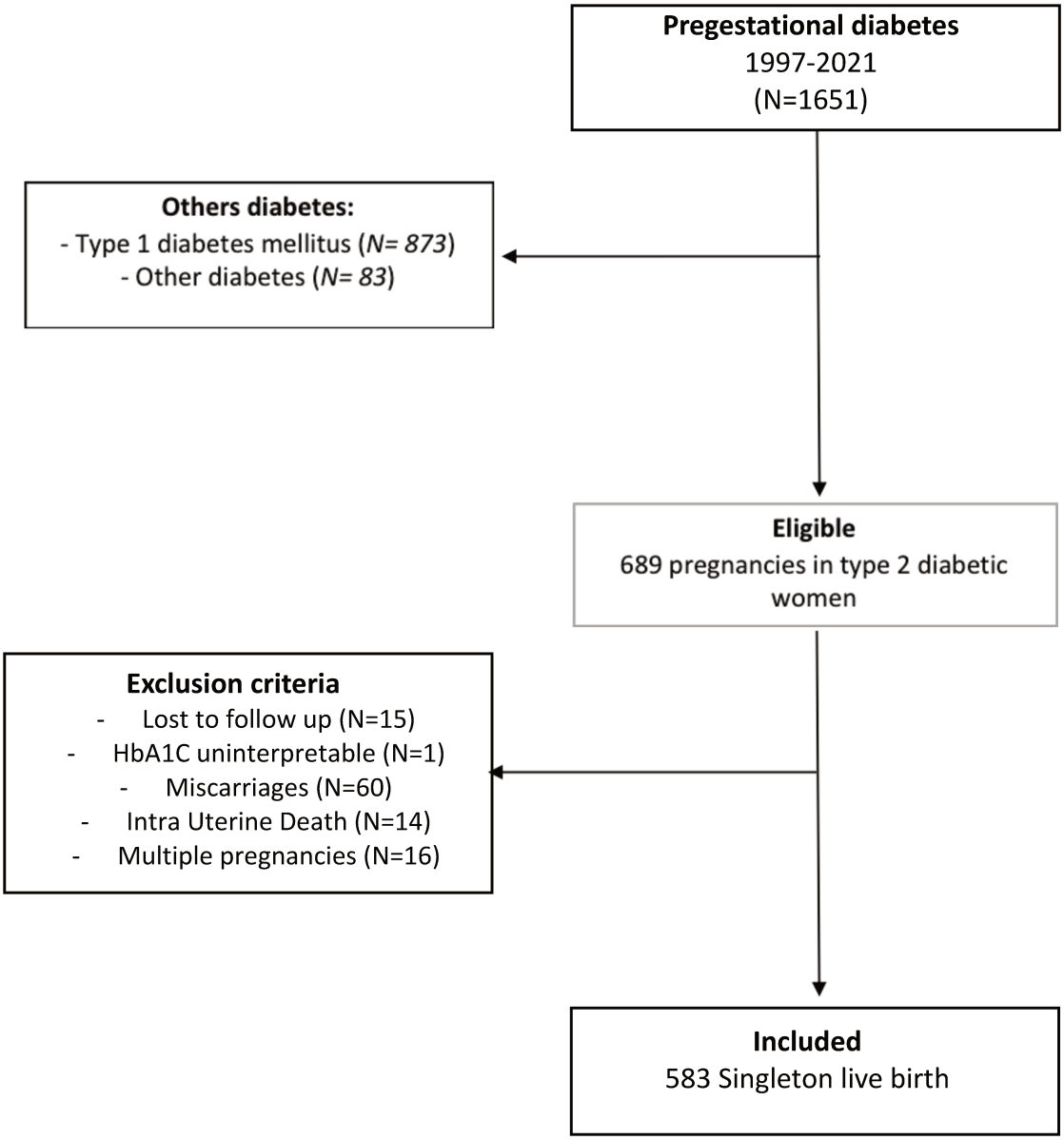


Figure 1: Patients enrollment flow chart

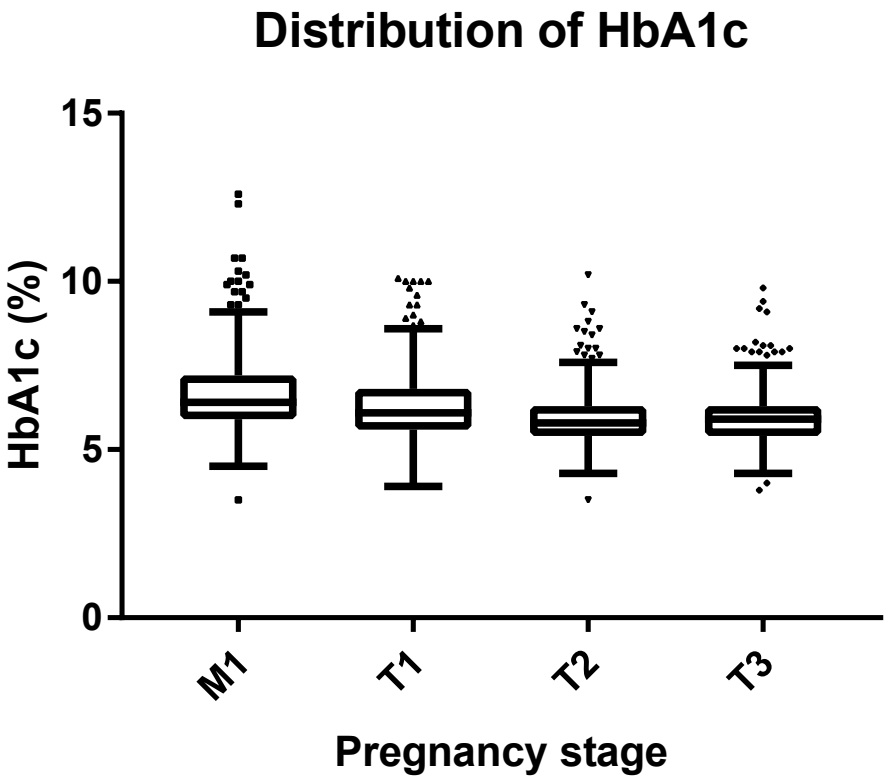


Figure 2 : Distribution of HbA1c (Tukey's boxplots) according to pregnancy stage during type 2 diabetes pregnancy.

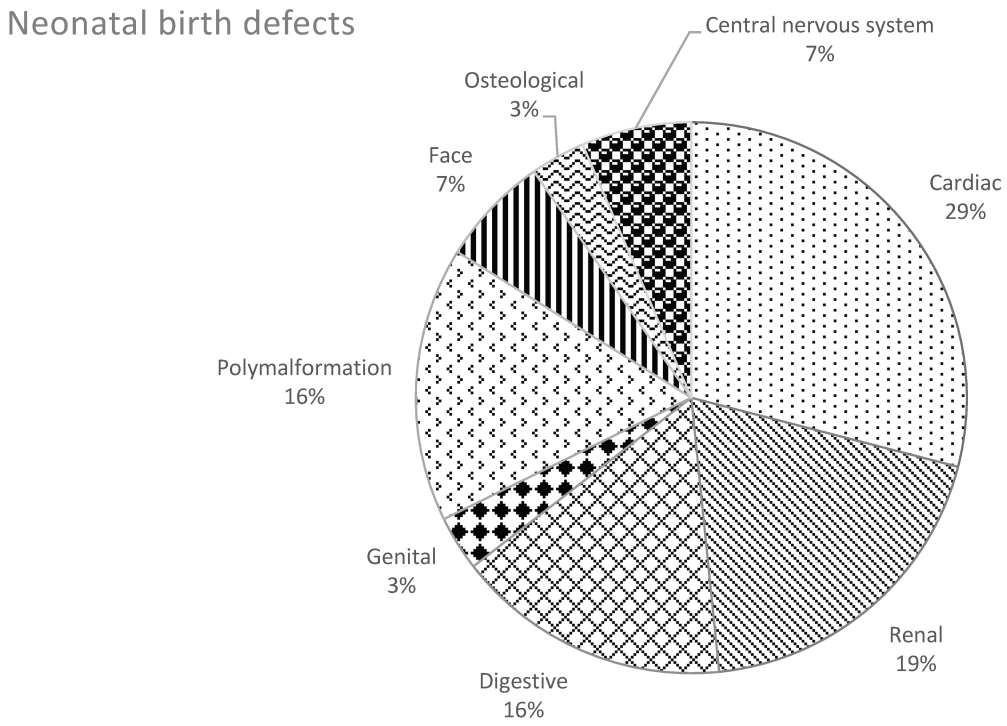


Figure 3: Types of neonatal birth defects.

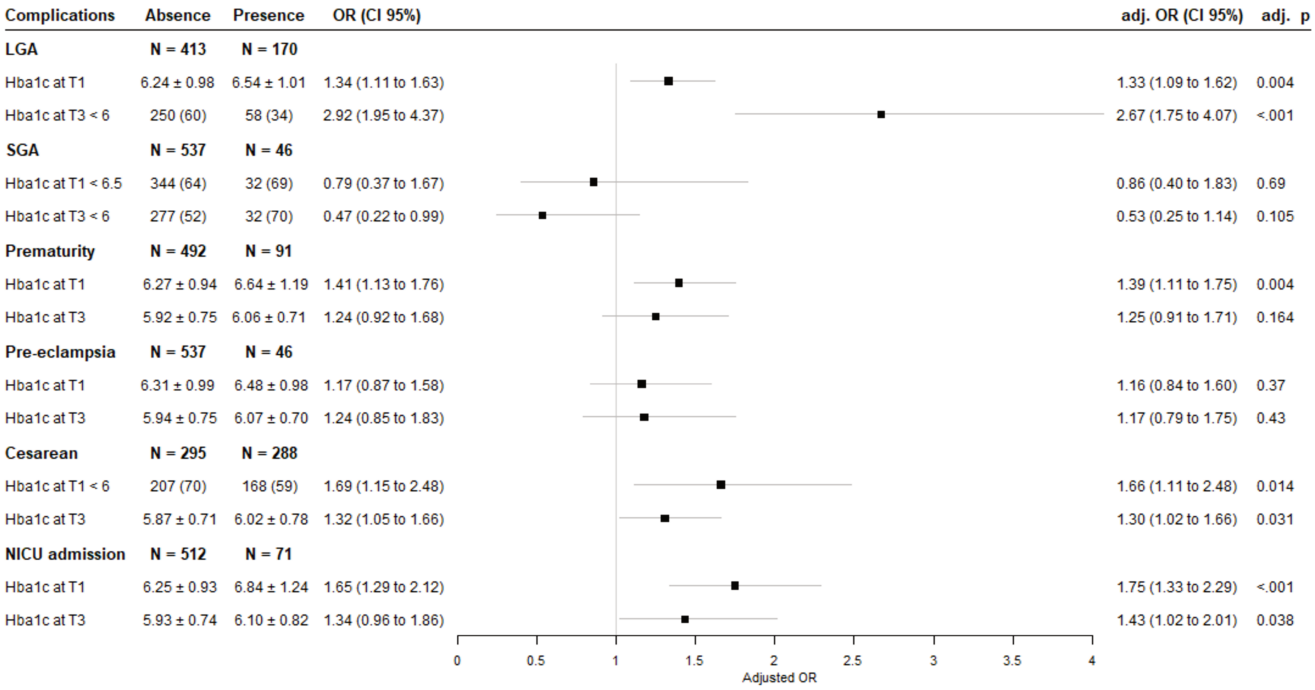


Figure 4: Association between adverse maternal/fetal outcomes and HbA1c during type 2 diabetes pregnancy.

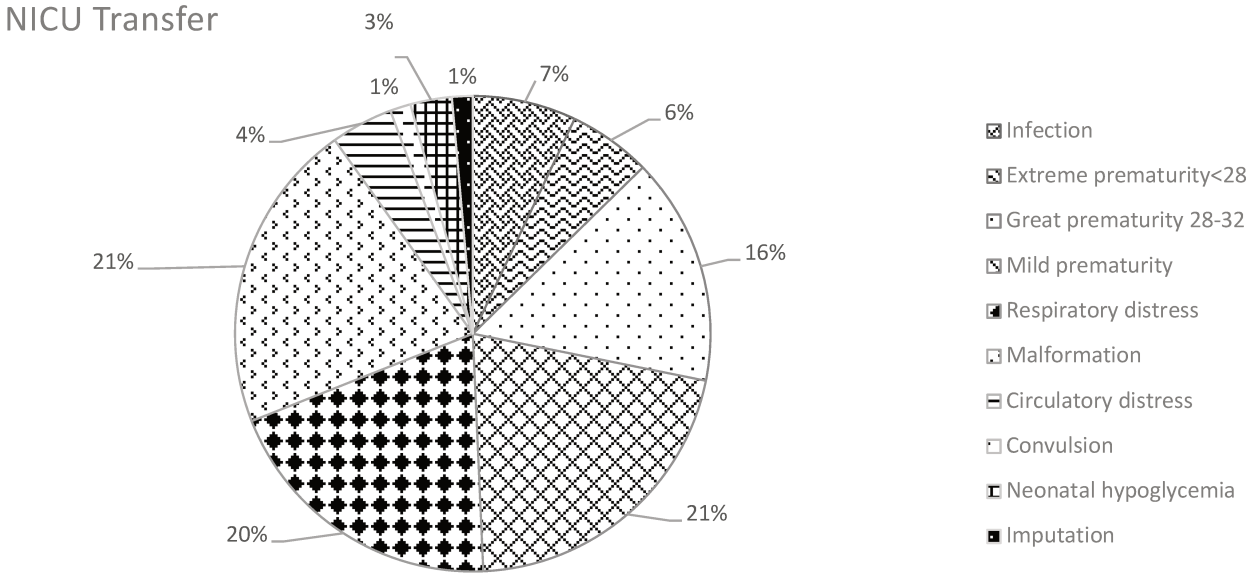


Figure 5: Indication of NICU transfer

Maternal characteristics *	N	Values
Age, years	583	33.9 ± 5.4
BMI before pregnancy, kg/m2	558	34.89 ± 7.10 [d]
BMI before pregnancy, N (%)	558	
Underweight		1 (0.2) [d]
Normal weight		33 (5.7) [d]
Overweight		95 (16.3) [d]
Obese		454 (77.9) [d]
Weight gain during pregnancy, kg	503	8.0 (3.0-12.0)
Weight gain during 1st trimester, kg	459	1.0 (0.0-3.0)
Weight gain during 3rd trimester, kg	452	4.0 (1.0-6.0)
Weight before pregnancy, kg	569	93.8 ± 20.3
Nulliparity, N (%)	583	101 (17.3)
Duration of diabetes, years	580	2.0 (0.0-5.0)
Diabetic vascular complication, N (%)	583	39 (6.7)
Diabetic retinopathy , N (%)	583	2.3 (17/583)
Diabetic nephropathy, N (%)	583	3.8 (22/583)
Diabetic neuropathy, N (%)	583	0.3 (2/583)
Smoking, N (%)	579	10.9 (63/579)
History of preeclampsia, N (%)	583	6.6 (39/583)
History of IUFD, N (%)	583	11.7 (68/583)
History of miscarriage, N (%)	583	29.0 (168/583)
History of miscarriage, med (IQR)		0.0 (0.0 -1.0)
History of Gestational diabetes, N (%)	583	42.4 (247/583)
History of macrosomia, N (%)	583	25.6 (149/583)
History of macrosomia, med (IQR)		0.0 (0.0 -1.0)
Hypertension before pregnancy, N (%)	583	16.0 (93/583)
Treatment before pregnancy, N (%)	582	
No treatment		55.3 (322/582)
Oral		37.3 (217/582)
Basal insulin		1.4 (8/582)
Multi-injections		4.1 (24/582)
Subcutaneous infusion		1.9 (1/582)
Treatment during pregnancy, N (%)	582	
Multi-injections		88.8 (517/582)
Subcutaneous infusion		6.2 (36/582)
Dietetary ,		5.0 (29/582)
Glycemic monitoring C/GSM, N (%)	583	94.7 (552) / 5.3 (31)
Contact with specialized nurses, N(%)	583	
Telephonic		82.2 (479/583)
Mydiabby		13.4 (78/583)
LibreView		4.5 (26/583)

Values are % (n/total), or mean ± SD, or median (IQR)
SD: standard deviation, IQR: interquartile range
BMI: body mass index
IUFD: intrauterine fetal death
C/GSM: Continuous glucose sensor monitoring

* : including IUFD
[d] : after multiple imputation

Table 1 : Baseline maternal characteristics

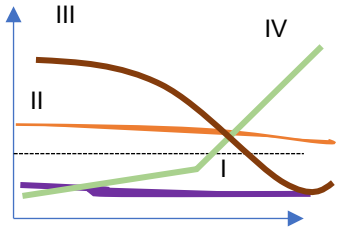
Groups of metabolic control		N = 583 (%)
Group I : HbA1C T1 < 6.5% and HbA1C T3 < 6.0%)		242 (41.6)
Group II : HbA1C T1 > 6.5% and HbA1C T3 > 6.0%)		141 (24.2)
Group III : HbA1C T1 > 6.5% and HbA1C T3 < 6.0%		66 (11.3)
Groupe IV : HbA1C T1 < 6.5% and HbA1C T3 > 6.0%		134 (22.9)

Table 2 : Groups of metabolic control

Maternal and fetal outcomes	**N**	**Values**	**After multiple imputation (N=583) ***
Mean HbA1C, %	394	6.0 ± 0.70	
HbA1C 1st trimester, %	444	6.3 0± 0.97	6.33± 0.99
HbA1C 2nd trimester, %	507	5.9 ± 0.8	
HbA1C 3rd trimester, %	522	5.93 ± 0.74	5.95 ± 0.75
Evolution of retinopathy, N (%)	583	32 (5.5)	
Proteinuria, N (%)	583	64 (11.0)	
Gravidic hypertension, N (%)	583	70 (12.0)	
Preeclempsia, N (%)	583	46 (7.9)	
Cesarean section, N (%)	581	287 (49.4)	288 (49.4)
Postpartum hemorrhage, N (%)	580	105 (18.1)	
Admission in ICU, N (%)	578	7 (1.2)	
Term, weeks	579	38.1 (37.6-38.9)	
Prematurity, N (%)	579	90 (15.5)	91 (15.6)
Shoulder dystocia, N (%)	580	8 (1.4)	8 (1.4)
Neonatal malformations, N (%)	579	31 (5.4)	31 (5.3)
SGA, N (%)	565	43 (7.6)	46 (7.9)
LGA, N (%)	565	164 (29.0)	170 (29.2)
Birth weight, grams	569		3329 ± 688.1
Admission in NICU	578	70 (12.2)	71 (12.2)

Table 3: Maternal and fetal/neonatal adverse pregnancy outcomes.

	Group I (n = 242)	Group II (n = 141)	Group III (n = 66)	Group IV (n = 134)	P
LGA					
No. (%)	42 (17,36)	58 (41,13)	17 (25,76)	53 (39,55)	
Unadjusted OR (95% CI)	1.00 (ref)	3.41 (2.08 to 5.59)	1.62 (0.81 to 3.24)	3.15 (1.82 to 5.46)	**< 0.001**
Adjusted OR (95% CI)	1.00 (ref)	2.94 (1.75 to 4.96)	1.50 (0.73 to 3.10)	2.97 (1.68 to 5.27)	**< 0.001**
Prematurity					
No. (%)	27 (11,16)	31 (21,99)	14 (21,21)	19 (14,18)	
Unadjusted OR (95% CI)	1.00 (ref)	2.19 (1.20 to 3.99)	2.17 (0.98 to 4.82)	1.34 (0.65 to 2.78)	**0,031**
Adjusted OR (95% CI)	1.00 (ref)	2.25 (1.21 to 4.19)	2.20 (0.98 to 4.92)	1.39 (0.67 to 2.89)	**0,034**
Pre eclampsia					
No. (%)	15 (6,2)	17 (12,06)	-	12 (8,96)	
Unadjusted OR (95% CI)	1.00 (ref)	2.07 (0.98 to 4.41)	"-"	1.51 (0.64 to 3.54)	0,11
Adjusted OR (95% CI)	1.00 (ref)	1.82 (0.83 to 3.99)	"-"	1.45 (0.61 to 3.46)	0,19
Caesarean					
No. (%)	105 (43,39)	85 (60,28)	35 (53,03)	63 (47,01)	
Unadjusted OR (95% CI)	1.00 (ref)	1.96 (1.25 to 3.05)	1.50 (0.77 to 2.91)	1.19 (0.75 to 1.89)	**0,034**
Adjusted OR (95% CI)	1.00 (ref)	1.86 (1.18 to 2.96)	1.43 (0.73 to 2.81)	1.15 (0.71 to 1.85)	0,076
Neonatal malformations					
No. (%)	5 (2,07)	14 (9,93)	5 (7,58)	7 (5,22)	
Unadjusted OR (95% CI)	1.00 (ref)	4.91 (1.62 to 14.90)	3.70 (0.87 to 15.71)	2.26 (0.68 to 7.56)	**0,035**
Adjusted OR (95% CI)	1.00 (ref)	"-"	"-"	"-"	
Intensive care unit admission					
No. (%)	18 (7,44)	25 (17,73)	16 (24,24)	12 (8,96)	
Unadjusted OR (95% CI)	1.00 (ref)	2.83 (1.41 to 5.65)	4.13 (1.63 to 10.42)	1.23 (0.47 to 3.24)	**0,013**
Adjusted OR (95% CI)	1.00 (ref)	3.41 (1.63 to 7.14)	4.59 (1.73 to 12.15)	1.31 (0.50 to 3.41)	**0,008**

Values are expressed as the number (%) and as OR (95% CI)

The different groups as defined as : group I, HbA1c at first trimester < 6.5% and < 6% at third trimester, considered as reference group; group II, HbA1c at first trimester ≥ 6.5% and ≥ 6% at third trimester; group III, HbA1c at first trimester ≥ 6.5% and < 6% at third trimester; group IV, HbA1c at first trimester < 6.5% and ≥ 6% at third trimester.

Abbreviations:
CI, confidence interval ; LGA, large for gestational age; SGA, small for gestational age
Adjusted for years of pregnancy (per group of 5 years) and for compliance with weight gain recommendations according to pre-gestational BMI
P for global comparisons

Table 4: Association of HbA1c with most individual adverse events according to glycemic control subgroups

IV- PERSPECTIVES :

Ces résultats nous indiquent que l'HbA1C est un outil fiable, pratique et peu coûteux du suivi glycémique, utilisable en pratique courante chez les patientes DT2 lors de la grossesse. Au-delà de son intérêt dans le contrôle glycémique, il semble exister une association forte entre niveaux d'HbA1c et complications maternelles et fœtales au cours des grossesses DT2.

L'objectif de notre travail était de déterminer si l'HbA1c pouvait être un facteur prédictif de la survenue de complications maternelles ou fœtales au 1er mais également au 3ème trimestre. La réponse est affirmative avec la mise en lumière de complications différentes entre le 1er et le 3ème trimestre. Nous avons mis en lumière que l'HbA1c est associée à la prématurité, aux admissions en réanimation néonatale, au LGA et à la césarienne. L'association entre HbA1c T1 et admissions en réanimation néonatale est un point intéressant, puisque cela nous permettra, peut -être, après avoir confortées ces données, d'individualiser la prise en charge des femmes DT2 les plus à risque. Cette individualisation de prise en charge pourrait donc se faire précocément (après résultats du 1er trimestre), dans l'objectif de réduire la fréquence de cet évènement indésirable de grossesse. Notons que l'analyse du groupe III, semble nous indiquer que malgré une optimisation de l'équilibre métabolique au 3ème trimestre (HbA1c ≤ 6%), ce risque persiste suggérant d'autre mécanisme d'implication. Des travaux semblent indiquer que l'observance incomplète du suivi est un mécanisme conduisant à ce sur-risque. L'étude de ce paramètre sera indispensable. Notre analyse en sous-groupes suggère que cela est valable pour les admissions en réanimation néonatales mais également pour les malformations congénitales (impact de l'équilibre glycémique sur l'organogénèse).

Ces résultats appuient l'importance du contrôle glycémique au cours de la grossesse et l'HbA1C est un outil de suivi à moyen terme idéal. Cependant, de nouveaux outils de suivi en temps réels comme la mesure continue de glucose et les plateformes de suivi glycémique en ligne sont utilisés depuis plusieurs années maintenant dans la prise en charge des grossesses des patientes DT1 avec pour résultat une diminution prouvée des complications maternelles et fœtales par un meilleur équilibre glycémique et une diminution de la variabilité glycémique. L'utilisation de ces outils tend à se

démocratiser dans le cadre de la grossesse DT2. Le CGSM pourrait être un outil intéressant permettant une diminution des complications materno-fœtales chez nos patientes mais des études doivent être mises en place pour en prouver les bénéfices au sein de la population diabétique de type 2. Dans ce cas, la mesure d'intérêt ne serait plus l'HBA1C mais plutôt le GMI (Glucose Management Indicator). Des études seront nécessaires pour déterminer la non-infériorité de ce nouveau marqueur en comparaison à l'HbA1c. De plus, les données concernant les hypoglycémies nous seraient plus facilement accessibles.

D'autres pistes n'ont pu être étudiées au cours de ce travail, notamment d'autres travaux prospectifs seront à instaurer afin d'étudier le rôle de l'insulino-résistance médiée par le surpoids et l'obésité en pré-conceptionnel, la prise de poids excessive pendant la grossesse ou encore la dyslipidémie au cours de ces grossesses, dans la survenue de ces complications materno-fœtales excessives au cours du DT2. Leurs rôles respectifs, en tant que mécanisme d'implication dans la persistance du risque de transfert néonatale en réanimation, malgré une correction de l'équilibre métabolique entre le 1er et 3ème trimestre, sera également à mettre en lumière (tout comme l'observance du suivi).

V- CONCLUSION :

Notre étude montre que l'hémoglobine glyquée est un outil de suivi fiable, reproductible, peu couteux utilisable au cours de la grossesse des patientes diabétique de type 2. Ce dosage est associé à la survenue de complications materno-fœtales telles que la prématurité, l'admission en réanimation néonatale, le LGA, la césarienne.

Le LGA semble déterminé principalement par le déséquilibre glycémique au cours du troisième trimestre de grossesse alors que les admissions en réanimation néonatale et les malformations congénitales semblent principalement déterminés par le déséquilibre glycémique au cours du premier trimestre de grossesse.

Ces données confirment l'importance de l'équilibre glycémique au cours de la grossesse mais également de la préparation et programmation en pré-conceptionnel tant sur l'équilibre glycémique, l'équilibre métabolique avec la gestion du poids la révision de l'ordonnance et la supplémentation en acide folique pour réduire au maximum le risque de survenues de complications materno-fœtales.

L'utilisation des nouvelles technologies avec la mesure continue de glucose, des plateformes de surveillance en ligne, l'étude du profil lipidique semblent être des pistes prometteuses afin d'y parvenir.

Notons que la correction de l'équilibre métabolique entre le 1er et le 3ème trimestre, objectivé au cours de ce travail pour le groupe III, ne permet pas de réduire les risques d'admissions néonatales en Réanimation suggérant donc d'autres mécanismes d'implication qu'il conviendra de mettre en lumière.

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Titre de la thèse: Relation entre l'HbA1C et les complications materno-fœtales au cours du diabète de type2.
Thèse - Médecine - Lille 2022
Cadre de classement : Diabétologie
DES: Endocrinologie- Diabétologie- Nutrition
Mots-clés : Grossesse, diabète de type 2, équilibre glycémie, HbA1C, complications materno-fœtales.

Résumé :
Contexte : Malgré l'optimisation de la prise en charge au cours de la grossesse, les diabétiques de type 2 présentent un sur-risque de complications materno-fœtales. L'objectif était d'évaluer l'impact de l'HbA1C des 1er et 3e trimestres, sur les complications maternelles et fœtales au cours des grossesses de patientes DT2.
Matériel et Méthode: Étude observationnelle, monocentrique, rétrospective, conduite au CHU de Lille entre 1997 et 2021. Nous avons recueilli les données métaboliques, les complications materno-fœtales au cours des grossesses de DT2. Après description de la pré-éclampsie, LGA, prématurité, malformations congénitales, transferts en réanimation néonatale (NICU), nous avons étudié leur association avec l'HbA1C du 1er et 3ème trimestre. Nous avons réalisé une analyse en sous-groupes afin d'étudier l'association entre la cinétique d'HbA1c au cours de la grossesse et les complications materno-foetales.
Résultats: 583 patientes incluses. Age moyen de 33.9 ± 5.4 ans, IMC prégestationnel de 34.9 ± 7.10 kg/m2. On décrivait 49.4% de césariennes, 15.6% de prématurité, 12.2% de transferts en NICU, de 5.3% de malformations congénitales et 29.2% de LGA. L'HbA1C du 1er trimestre est associée au LGA (OR 1.33 ; 95%IC 1.09 -1.62 ; p=0.004), à la prématurité (OR 1.39 ; 95%IC 1.11 -1.75 ; p=0.004), à la césarienne (OR 1,66 ; 95%IC 1.11 -2.48 ; p=0.014) et aux admissions en NICU (OR 1.33 ; 95%IC 1.75 -2.29 ; p<0.001). L'HbA1C du 3e trimestre est associé au LGA (OR 2.67 ; 95%IC 1.75 -4.07 ; p<0.001), la césarienne (OR 1.30 ; 95%IC 1.02 -1.66 ; p=0.031), aux admissions en NICU (OR 1.43 ; 95%IC 1.02 -2.01 ; p=0.038). L'analyse en sous-groupe retrouve qu'en cas de déséquilibre tardif, pour chaque augmentation de 0,1 % de l'HbA1c au 1er trimestre, les risques de prématurité (OR 1.39 ; 95%IC 1.11 -1.75 ; p=0.004) et d'admission NICU (OR 1.75 ; 95%IC 1.33 -2.29 ; p<0.001) augmentent. En cas de déséquilibre au 3ème trimestre, le risque de LGA est majoré (OR 2.67 ; 95%IC 1.75 -4.07 ; p<0.001).
Conclusion: L'HbA1C est associée aux complications materno-fœtales. En cas de déséquilibre glycémique précoce, l'élévation de l'HbA1C du 1er trimestre est associée à un sur-risque de transfert NICU et de prématurité, même en cas de correction de l'équilibre glycémique ultérieur. En cas de déséquilibre tardif, le niveau d'HbA1c est un marqueur du risque de LGA.

Composition du Jury :
Président : Pr Damien Subtil
Assesseurs : Pr Anne VAMBERGUE
Pr Laurent STORME
Directeur de thèse : Dr Madleen Lemaitre