UNIVERSITE DE LILLE

FACULTE DE MEDECINE HENRI WAREMBOURG

Année : 2020

THESE POUR LE DIPLOME D'ETAT

DE DOCTEUR EN MEDECINE

Y a-t-il un intérêt à effectuer un dosage d'HbA1c au moment du diagnostic de diabète gestationnel ?

Présentée et soutenue publiquement le 19 mai 2020 à 18 heures
au Pôle Formation

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Abréviations

BMI : Body mass index

DIP : Diabete In Pregnancy

DG : Diabète Gestationnel

DPG : Diabète Pré Gestationnel

DT1 : Diabète de Type 1

DT2 : Diabète de Type 2

GAJ : Glycémie A Jeun

GDM : Gestational Diabetes Mellitus

GWG : Gestational Weight Gain

HAPO : Hyperglycemia and Adverse Pregnancy Outcomes

HGPO : Hyperglycémie Provoquée Par Voie Orale

HbA1c : Hémoglobine A1c

IMC : Indice de Masse Corporelle

IUGR : Intrauterine Growth Retardation

LGA : Large-for-Gestational-Age

OGTT: Oral Glucose Tolerance Test

SA : Semaines d'aménorrhée

SGA : Small-for-Gestational-Age

SMBG: Self-monitoring of Blood Glucose

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I) Résumé

Introduction

Avec la situation actuelle et l'augmentation de la prévalence du DG, une stratification des patientes est nécessaire afin d'identifier celles étant le plus à risque de complications maternofoetales. Il n'est pas clairement démontré qu'un seuil d'Hba1c serait utile pour prédire la survenue de complications maternofoetales pendant la grossesse. De plus, on ne sait pas si un tel seuil d'Hba1c diffère en cas de DG précoce ou tardif. Les objectifs sont donc d'examiner la relation entre l'Hba1c et la survenue de complications maternofoetales et de déterminer si ce seuil d'Hba1c diffère en fonction du terme du diagnostic de DG.

Matériels et Méthodes

Etude basée sur une cohorte de 4384 femmes atteintes de DG avec facteurs de risque entre 2011 et 2018. Les patientes ont fait l'objet d'un dépistage selon les critères de l'IADPSG. L'HbA1c était mesurée au moment de la prise en charge du DG. Nous avons évalué l'association de l'Hba1c avec les complications maternofoetales à l'aide de modèles de régression logistique avant et après ajustement sur les facteurs de risque prédéfinis de DG. L'Hba1c était considérée comme une variable catégorielle divisée en 5 classes prédéfinies : ≤4,5 %, 4,6-4,9 %, 5-5,5 %, 5,6-5,9 % et >5,9 %. Les résultats ont été exprimés en rapport de cotes (RC) et en intervalles de confiance (IC) à 95 %, comparés à la catégorie de référence Hba1c ≤4,5 %.

Résultats

L'HbA1c a été dosée en moyenne à 25 +/- 7.5 SA pour une valeur de 5.2% +/- 0.4. 41.6% des patientes ont présenté au moins une complication parmi la macrosomie, le SGA, la pré éclampsie, la prématurité, l'admission en unité de soins intensifs néonataux et la dystocie

des épaules (définissant le critère composite). Une valeur d'HbA1c ≥ 5.6% est associée à une augmentation du risque de macrosomie (OR pour 5.6-5.9 = 2.12 [IC 95% = 1.29-3.46] et OR pour >5.9 = 2,06 [IC 95% = 1.14-3.7]) et de césarienne (OR pour 5.6-5.9 = 1.64 [CI 95% = 1.06 - 2.53] ; OR pour >5.9 = 1.58 [CI 95% = 0.93- 2.7]). La prévalence de la prématurité augmente lorsque le seuil d'HbA1c est ≥ 5.9% (OR=3.33 [IC 95% = 1.27-8.71]). Après ajustement sur le nombre de facteurs de risque, nous confirmons ces résultats pour la macrosomie, la prématurité ($p<0.001$), et la césarienne ($p=0.020$). L'Hba1c est restée significative pour le critère composite même après ajustement. Ces analyses ont été effectuées chez les DG précoces (diagnostiqués avant 20 SA) et tardifs (après 20 SA) avec des résultats similaires.

Conclusion

Ces résultats montrent qu'un dosage d'HbA1c au moment du diagnostic est utile pour identifier les patientes les plus à risque de complications maternofœtales en cas de DG avec facteurs de risque. Ceci permettrait de moduler et de personnaliser la prise en charge pour chaque patiente. En revanche il ne semble pas apporter d'intérêt supplémentaire que le DG soit précoce ou tardif, en dehors de l'identification d'un DPG.

II) Introduction

a. Généralités : Diabète et grossesse.

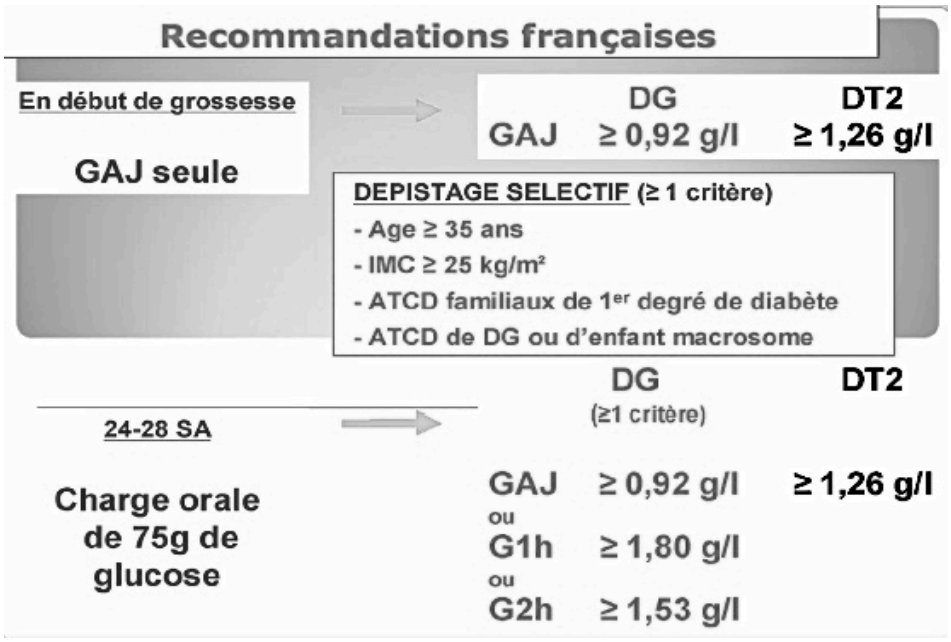
Le diabète gestationnel est défini par l'OMS comme un trouble de la tolérance glucidique conduisant à une hyperglycémie de sévérité variable, débutant ou diagnostiqué pour la 1ère fois pendant la grossesse, quelque soit le traitement nécessaire et l'évolution dans le post-partum (1). Cette définition distingue en réalité deux entités : d'une part la forme qui survient uniquement durant la grossesse et que l'on nomme le diabète gestationnel (DG) et d'autre part les diabètes préexistants à la grossesse, tels que le diabète de type 1 (DT1) ou le diabète type 2 (DT2), qui persisteront après l'accouchement. Une nouvelle catégorie de troubles glucidiques a été définie lorsque le diabète est diagnostiqué pendant la grossesse, appelé "Diabete In Pregnancy" (DIP). Il concerne les patientes avec des valeurs glycémiques supérieures aux seuils définissant le diabète en dehors de la grossesse : glycémie plasmatique à jeun ≥1.26 g/l et/ou glycémie à 2 heures ≥2g/l et/ou HbA1c ≥6.5%.

Le DG est l'une des complications les plus fréquentes de la grossesse. En 2012, une étude portée sur 3 353 dyades mère-enfant issues d'un échantillon aléatoire d'enfants nés dans 136 maternités tirées au sort en France métropolitaine, a estimé la prévalence du DG était à 8%. La prévalence était plus élevée en cas de facteurs de risque associés : chez les femmes âgées de 35 ans et plus (14,2%), en surpoids/obèses (11,1 et 19,1% respectivement) et avec des antécédents de DG (50,0%). (2)

Les critères diagnostics du DG ont été modifiés à plusieurs reprises au cours des dernières décennies. Après l'étude HAPO (Hyperglycemia and Adverse Pregnancy Outcome) (3)

publiée en 2008 qui a montré une corrélation positive entre l'hyperglycémie maternelle et les complications périnatales, un consensus international par un panel d'experts (IADPSG) a été proposé sur les modalités de dépistage du DG (4). Après ces publications, un groupe d'experts français mené conjointement par la Société Francophone de Diabétologie (SFD), le Collège National des Gynécologues Obstétriciens Français (CNGOF) et la Société de Périnatologie et de Néonatologie (SFP) ont émis des recommandations françaises de dépistage du DG (5-6). L'hyperglycémie provoquée par voie orale est le gold standard pour le diagnostic de DG au 6ème mois de la grossesse. Par contre le diagnostic sur la glycémie à jeun au début de la grossesse reste contesté sur le plan international (7).

Le dépistage et le diagnostic du DG selon les recommandations françaises sont résumés dans la Figure suivante.



Journal de Gynécologie Obstétrique et biologie de la Reproduction, Diabete et Metabolism 2010

Ces nouvelles modalités de dépistage tendent à accroitre l'incidence du DG (8). En effet dans certaines études, la prévalence du DG sur l'ensemble de la cohorte étudiée est à 17,8%, avec de grandes variations selon les centres (9.3% en Israël vs 25.5% aux Etats-Unis) (9). La prévalence du DG est bien sûr corrélée à l'importance des facteurs de risque si bien que le dépistage du DG chez les femmes sans facteur de risque est débattu (10). Cosson et *al*. ont d'ailleurs démontré que la présence de facteurs de risque était significativement associée au DG et prédictive de complications maternofoetales. Ils suggèrent ainsi que l'obésité, seul facteur de risque modifiable, peut être une cible pour l'amélioration du pronostic du DG (11).

b. Enjeux de la prise en charge précoce du DG

Le DG est à l'origine de complications maternelles et fœtales corrélées de façon positive et linéaire au degré de l'hyperglycémie initiale (1).

La macrosomie est la principale complication du diabète gestationnel. Deux termes sont utilisés pour définir l'excès de croissance foetale. La macrosomie définie par un poids de naissance à terme supérieur ≥ 4000 grammes, et le LGA applicable lorsque le poids est ≥ au 90° percentile en fonction de l'âge gestationnel. L'étude françaises AUDIPOG a établi des courbes de référence pour l'âge gestationnel en fonction du sexe foetal (12). Dernièrement, une courbe de référence révisée pour les États-Unis, à partir des données du National Center for Health Statistics de 2011, a fourni une mise à jour nationale sur le poids à la naissance (14). Les valeurs de poids foetaux du 50ème, 69ème et 95ème percentile en fonction de l'âge gestationnel sont montrés dans le tableau ci joint.

Gestational Age	Birth Weight (g)		
	50th Percentile	90th Percentile	95th Percentile
37	3,025	3,612	3,818
38	3,219	3,799	3,995
39	3,374	3,941	4,125
40	3,499	4,057	4,232
41	3,600	4,167	4,340
42	3,686	4,290	4,474

Modified from Duryea EL, Hawkins JS, McIntire DD, Casey BM, Leveno KJ. A revised birth weight reference for the United States. Obstet Gynecol 2014; 124:16–22.

L'excès de croissance s'explique par l'hyperglycémie et l'hyperinsulinisme fœtal provoquant un dépôt adipeux sur les parties supérieures du corps (macrosomie disharmonieuse). L'obésité maternelle, l'ethnie et la prise de poids pendant la grossesse sont des facteurs de risque surajoutés à la macrosomie.

La naissance d'un enfant macrosome majore la morbidité maternelle et fœtale essentiellement dû aux pathologies traumatiques, aux hémorragies du post-partum et aux complications infectieuses pendant l'accouchement. Les enfants macrosomes sont eux plus susceptibles d'avoir des troubles métaboliques à type d'hypoglycémie, de polyglobulie ou d'acidose (15).

D'après les dernières recommandations américaines, le déclenchement avant 39SA est déconseillé suite au manque de preuve sur l'avantage de la réduction du risque de dystocie des épaules comparé aux méfaits d'un accouchement précoce. La césarienne reste indiquée dès lors que le poids foetal estimé excède 4500g chez les femmes diabétiques (16).

L'HTA gravidique et la pré-éclampsie, définie par une hypertension après 20 SA associées à une protéinurie, une dysfonction d'organe ou un retard de croissance foetale (17), sont également plus fréquentes chez les femmes ayant un diabète gestationnel. Ceci est en partie expliqué par la présence d'un terrain similaire. En effet le surpoids et l'obésité sont des

facteurs de risque de pré éclampsie indépendamment de l'hyperglycémie maternelle. Leur association avec le DG augmente le risque de pré-éclampsie en comparaison au patiente DG à IMC normal (18). En revanche le déséquilibre glycémique au premier trimestre de grossesse semble augmenter le risque de survenue d'une pré-éclampsie chez les patientes avec un diabète préexistant (19).

Les taux d'extraction instrumentale, de déchirure périnéale sévère et d'hémorragie du post-partum ne sont pas modifiés par le DG (18).

Les complications néonatales liées spécifiquement au DG sont plus rares. Il n'existe pas de risque de malformations néonatales et l'augmentation de décès périnataux n'est pas démontrée. En revanche ce risque est présent lors de l'existence d'un diabète méconnu.

Le lien entre le DG et la survenue de complications périnatales est cependant bien établi et largement accepté. En effet, les nouveaux nés de mère présentant un DG naissent plus souvent prématurés et par césarienne, en lien avec l'augmentation de la croissance fœtale (20).

Le risque d'asphyxie néonatale, toutes causes confondues, est difficile à apprécier. Il n'existe pas suffisamment de données dans la littérature pour expliquer le lien entre le DG et les troubles respiratoires néonataux. Certaines études tendent toutefois à montrer que l'hyperglycémie allant jusqu'à l'insulinothérapie majore le risque de complications respiratoires néonatales (21).

La prévalence de l'hypoglycémie néonatale sévère en cas de DG est faible. Ce risque est directement lié au degré d'hyperglycémie maternelle et à l'hyperinsulinisme fœtale qui en

résulte. Il reste cependant difficile à appréhender en raison de l'hétérogénéité de la définition d'hypoglycémie dans les différentes études (18).

Le traitement spécifique du DG repose sur la diététique, l'auto-surveillance glycémique, et l'insulinothérapie si nécessaire. Toutes les publications s'accordent à dire que la prise en charge du DG permet de diminuer l'incidence des complications maternofœtales (22-23), d'où l'intérêt d'un dépistage précoce des patientes à risque.

c. HbA1c pendant la grossesse

L'HbA1c est un dosage biologique simple, reproductible et que l'on connaît, en dehors de la grossesse, un facteur prédictif de complications du diabète (24).
Chez les patientes présentant un diabète et un désir de grossesse, un taux d'HbA1c supérieur à 6,5% en pré-conceptionnel a un impact sur la survenue des malformations fœtales et la mortalité périnatale (25). Dans le contexte du DG, l'HbA1c n'a pas de rôle proprement défini. Le diagnostic de DG se fait uniquement sur les valeurs glycémiques, soit par la glycémie à jeun (définissant le DG précoce) ou par les valeurs de l'HGPO (DG tardif).

L'un des premiers facteurs limitant son interprétation est la modification de l'HbA1c avec les modifications physiologiques de la grossesse. L'augmentation du renouvellement de l'hémoglobine et la carence martiale liée à la grossesse entrainent en effet une sous-estimation de l'HbA1c (26). Ainsi dans leur étude Connor *et al.* s'accordent à montrer que les normes d'HbA1c sont significativement diminuées au premier et deuxième trimestres en comparaison aux patientes non enceintes (seuil de 4,3-5,4% au premier trimestre, au

deuxième trimestre 4,4-5,4%, au troisième trimestre de 4,7-5,7%, *vs* 4,8–5,5% en dehors de la grossesse) (27).

Concernant le lien avec les complications materno-foetales, Hughes *et al.* (28) ont démontré qu'une HbA1c ≥ 5,9% était prédictive de LGA, de prématurité, de pré-éclampsie, de malformations congénitales ainsi que de mort *in utero*. Cependant chez ces mêmes patientes avec une HbA1c comprise entre 5,9 et 6,4%, 46.6% avaient un test d'HPGO anormal en post partum (13% en faveur d'un diabète de type 2 et 32% d'intolérance aux hydrates de carbone), ce qui est en faveur d'un DPG plutôt que d'un réel DG.
Plusieurs autres études ont analysé le lien entre l'HbA1c et la survenue de complications maternofoetales. Une synthèse des résultats est présentée dans le tableau ci-dessous (28-34). L'HbA1c semble donc être un marqueur de pronostic maternofoetal, mais encore avec une grande variabilité des seuils d'HbA1c fixés.

Ainsi à l'heure actuelle, le seul intérêt reconnu au dosage de d'HbA1c au cours du DG reste la suspicion d'un DPG (6). La valeur seuil fixée est de 6,5%, bien que certaines études évoquent la possibilité d'un seuil plus bas d'HbA1c. En 2020, l'ADA a d'ailleurs retenu une valeur d'HbA1c ≥ 5.7% (5.7-6.4%) dans les critères diagnostics du pré diabète en dehors de la grossesse. A ce jour, l'ADA ne s'est pas positionné si un seuil d'HbA1c permettrait de poser le diagnostic de DG ni sur un seuil prédictif de complications maternofoetales au cours du DG (35).

Etudes étudiant le lien entre l'HbA1c et les complications maternofoetales.

Auteur Année Ref	n	Diagnostic de DG	HbA1c moyenne	Terme HbA1c	% insulinées	Complications associées à l'HbA1C	Seuil
Capula et al. J.Endocrinol. Invest. 2013 (29)	148	HGPO 100g entre 24 et 28 SA selon ACOG	5.3%	28SA	23.6 %	survenue d'une complication : HTA, LGA, mortalité foetale.	>5.3%
Hughes et al. Diabetes care 2014 (28)	16122	HPGO 75g av 20 SA IADPSG	5.3%	47 jours	NC	prématurité pré-éclampsie LGA dystocie des épaules mortalité foetale	≥ 5,9%
Ye et al. Diabete Res Clin Pract. 2016 (30)	413	HGPO 75 g entre 24 et 28 SA IADPSG	5.1%	25.9SA	NC	Une majoration d'HbA1c de 1% augmente le risque de 2.24 fois la prématurité, 1.56 fois l'hyperbilirubinémie, 2.99 fois le risque d'asphyxie néonatale.	Pas de seuil fixé
Barquiel et al. 2016 (31)	2037	HGPO 100g (à jeun 5.8 mM; 1 h, 10.6 mM; 2 h, 9.2 mM; 3 h, 8.1 mM) National Diabetes Data Group (NDDG) criteria	5.2%	27 SA	NC	LGA et complications néonatales (hypoglycémie, hyper bilirubinémie, DRA, traumatismes obstétricaux, mortalité périnatale)	5%
Sweeting et al. JCEM 2017 (32)	844	HGPO 75g entre 24 et 28 SA GAJ ≥5.5 mmol/l (99mg/dl) à 2 heure ≥8.0 mmol/l (145mg/dl) (ADPS)	5.3%	17.6 SA +/- 3.3 (DG précoce)	64.8 % terme début 24.5 sa	LGA Macrosomie césarienne HTA (pré-éclampsie ou TA >140/90mmhg ss protéinurie)	>5.6% >5.9% >5.9% >5.9%

Sweeting et al. JCEM 2017 (32)	2254	idem	5.3%	29.4 SA +/-2.6 (standard)	45.9 % terme début 32.9 sa	LGA macrosomie césarienne HTA (pré-éclampsie ou TA >140/90mmhg ss protéinurie)	>5.9% >5.9% >5.6% >5.9%
Mane et al. JCEM 2017 (33)	1228	HPGO 50g + HPGO 100g (NDDG)	NC	NC	NC	Macrosomie pré-éclampsie	>5.9% >5.9%
Riche et al. SFD 2019 (34)	201	SFD/CNGOF guidelines	5.3%	NC	46%	Survenue d'une complication parmi : macrosomie, césarienne, prématurité, DRA, dystocie, pré-éclampsie, transfert en néonatologie.	>5.2%

d. Objectif et design de l’étude.

Compte tenu de l'augmentation de la prévalence du DG qui contraste avec les limitations de ressources actuelles, l'identification précoce des patientes à risque de complications permettrait aux soignants une prise en charge optimisée. Le gold standard pour dépister le DG en France est l'HGPO au 6ème mois de grossesse. Le diagnostic de DG ne se fait pas sur l'Hba1c. Cependant en dehors de la grossesse, l'HbA1c est un marqueur facilement réalisable, prédictif des complications du diabète. Elle pourrait donc aussi avoir un rôle dans la prédiction des complications maternofœtales dans le DG, en dehors de l’identification d’un état de diabète préexistant et méconnu.

Le but de l’étude est donc d'étudier chez des patientes DG avec facteur de risque s’il existe un seuil d’HbA1c prédictif de complications maternofœtales.

Pour cela, nous avons recensé l’ensemble des patientes prises en charge au Centre Hospitalier Universitaire de Lille pour un DG entre le 2 février 2011 et le 21 décembre 2018. Chaque patiente présentant au moins un facteur de risque de DG suivant a été inclue : un IMC > ou égal à 25, un âge > ou égale à 35 ans, un antécédent familial au premier degré de diabète, un antécédent personnel de macrosomie ou de DG. Les patientes ne présentant aucun de ces facteurs de risque ainsi que celle ou l’HbA1c était supérieur ou égale à 6,5% ont été exclues. Nous avons ainsi recueilli et analysé les données démographiques, diabétologiques, métaboliques, obstétricales et néonatales de 4383 grossesses.

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

III) Article

IS HbA1c DOSAGE RELEVANT AT GESTATIONAL DIABETES DIAGNOSIS OUTSIDE IDENTIFY A PREEXISTING DIABETES MELLITUS?

ABSTRACT

Objective

The current situation and increasing prevalence of gestational diabetes necessitates risk stratification directing limited antenatal resources to those at greatest risk. It is unclear whether HbA1c threshold has utility in predicting adverse outcomes in GDM. Furthermore, it is unknown if such an HbA1c threshold exists and/or differs among women diagnosed and treated for GDM prior to 20 week's gestation. The aims of the study were to examine the relationship of HbA1c at GDM diagnosis with adverse pregnancy outcomes and to determine if this HbA1c risk threshold differs in women diagnosed with early vs standard GDM, in a large treated cohort.

Research design and methods

This was a cohort study based on 4384 women with GDM in France, between 2011 and 2018. Women with risk factors were screened for GDM with fasting plasma glucose at the first prenatal visit and between 24-28 weeks with a 75-g OGTT using the IADPSG criteria. Pregnant women underwent an HbA1C measurement at the time of GDM management. We assessed the association of HbA1c with pregnancy outcomes using logistic regression models before and after adjustment in predefined risk factors of GDM. We examined the associations considering HbA1c as categorical variables using five pre-specified HbA1c classes: ≤4.5%, 4.6-4.9%, 5-5.5%, 5.6-5.9% and >5.9%. The results were expressed in odds

ratios (OR) and their 95% confidence intervals (CI), calculated using HbA1c ≤ 4.5% as reference.

Results

HbA1c was measured at a median of 25 +/- 7.5 weeks gestation. Mean baseline HbA1c was 5.2% +/-0.4. 33 % of patients were treated with insulin. 41.6% of women had at least one complication from macrosomia, SGA, preeclampsia, preterm delivery, neonatal intensive care unit admission and shoulder dystocia (defining the composite criterion). A threshold HbA1c ≥5.6% identifies women with a greater need for surveillance for macrosomia (OR for 5.6-5.9 = 2.12 [CI 95% = 1.29 to 3.46]; OR for >5.9 = 2.06 [CI 95% = 1.14 to 3.70]) and cesarean (OR for 5.6-5.9 = 1.64 [CI 95% = 1.06 to 2.53]; OR for >5.9 = 1.58 [CI 95% = 0.93 to 2.7]). It is the same for preterm delivery with a threshold HbA1c >5.9% (OR = 3.33 [CI 95% = 1.27 to 8.71]). After adjustment for GDM risk factors, we confirmed these results for macrosomia, preterm delivery ($p<0.0001$), and cesarean ($p=0.020$). HbA1c remained significant for Adverse Pregnancy Outcome Composite even after risk factor adjustment ($p<0.0001$). These analyses were carried out in the early GDM (diagnosed before 20 weeks gestation) and in the late GDM (after 20 weeks gestation) with similar results.

Conclusions

Our finding suggests that a single HbA1c taken at diagnosis for gestational diabetes mellitus with risk factor may be a useful pragmatic guide to identify women at risk for adverse outcomes. These clinical approaches could dichotomized women into high- and low-risk models of care at diagnosis.

INTRODUCTION

Hyperglycaemia in pregnancy includes both gestational diabetes mellitus (GDM) and overt diabetes (OD), also called ‘diabetes in pregnancy’. The OD category was introduced in the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations to capture unknown but preexistent type 2 diabetes (T2D) in pregnancy, and is now widely used (4).

The French-speaking Society of Diabetes (SFD) and French National College of Obstetricians and Gynecologists (CNGOF) proposed in 2010 a consensus on screening based on risk factor. Hyperglycaemia is defined according to IADPSG/WHO criteria (4), as these guidelines have been endorsed in France. Early screening constitutes a fasting plasma glucose (FPG) measurement, whereas late screening includes a 75-g oral glucose tolerance test (OGTT), with measurement of FPG and plasma glucose levels at 1 h and 2 h after glucose intake (1-h PG and 2-h PG, respectively). Oral glucose tolerance test and fasting plasma glucose are the gold standard tests for diagnosing GDM (7). However, these tests require at least 8h fasting and are time-consuming. Moreover, OGTT needs a minimum of two blood sample collections.

HbA1c represents a well-established tool in the management of both T1D and T2D, reflecting the average blood glycemic levels over several weeks and it’s a strong predictor of diabetes complications. An HbA1c threshold ≥6.5% is recommended for diagnosis preexisting diabetes in pregnancy (6). However, contrary to the non-pregnant state, HbA1c determination is not even considered normal in the current practice. The optimal HbA1c level in pregnancy is likely to be lower since the HbA1c level falls in the first and second trimester (4,3 to 5,4% in

the first trimester, 4,4 to 5,4% in the second, 4,7 to 5,7% in the third, *vs* 4,8 to 5,5% outside pregnancy) (24).

The association between the HbA1c and pregnancy outcomes has been reported in previous studies. Among these studies, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study has provided that HbA1c baseline and OGTT were significantly associated with adverse pregnancy outcomes; however, the association was stronger for the OGTT than the HbA1c. So, they concluded that the HbA1c baseline was not a useful alternative to an OGTT in pregnant women (36).

However, more recent studies have linked the HbA1c to adverse pregnancy outcomes using cutoff points for the HbA1c. First, Hughes et al. (28) identified in early GDM that an HbA1c threshold ≥5.9% was predictive of adverse pregnancy outcomes. Indeed it increased the risk of preeclampsia, shoulder dystocia, perinatal death, preterm delivery, induction of labor, LGA and major congenital abnormality.

Thus, OGTT is gold standard and no single test can replace it in diagnosing GDM. However, HbA1c testing is an attractive option, reproductible, and can be added to the routine early pregnancy laboratory test.

The purpose of this study was to examine the potential relationship between antenatal HbA1c at GDM diagnosis and adverse pregnancy outcomes. The challenge was to determine the optimal HbA1c threshold in order to identify women with increased risk of adverse pregnancy outcomes who may potentially benefit from an earlier adapted management.

RESEARCH DESIGN AND METHODS

This single-centre observational study took place at the University hospital of Lille, France, and based on electronic medical records, including the metabolic and obstetrical data that are routinely completed in the delivery of every woman giving birth. These data are collected and checked during the pregnancy. According to French law, patients are informed that care related data may be used for research purposes unless the patient opposes such use. These data were analysed anonymously, and our database was declared to the French Committee for computerized data (CNIL). In this observational cohort study, we included all women with GDM who gave birth between January 2011 and 2018.

We included patients with at least one risk factor of GDM: BMI greater than or equal to 25 kg/m2, age above 35 years, history of GDM, macrosomia or familial history of diabetes. The GDM diagnosis was defined based on the SFD/CNGOF guidelines: during first-trimester diagnosis was accepted if fasting plasma glucose level was greater than or equal to 0.92g/l (5.1 mmol/l). In case of non-pathological measurement, a standard 75 g 2- h OGTT was performed between 24 and 28 SA, with the following diagnosis criteria to define GDM: fasting plasma glucose ≥0.92g/l (5.1mmol/l), 1h plasma glucose ≥1.80 g/l (10mmol/l), or 2h plasma glucose ≥1.53g/l (8.5mmol/l). We have differentiated early GDM (diagnosed before 20 weeks of gestation) and late GDM (diagnosed after 20 weeks of gestation).

The exclusion criteria were abortion, twin pregnancy and an HbA1c dosage over 6.5%, excluding all other types of diabetes mellitus including type 1 diabetes, monogenic diabetes and secondary diabetes. The rationale for these exclusion criteria is based on the fact that it is well documented that women with preexisting diabetes, HbA1c ≥6.5% and women with a twin pregnancy are at increased risk of adverse pregnancy outcomes.

Once the diagnosis has been confirmed, patients received an appointment for an initial consultation in day hospital where we devote a large part to the explanation of preventive hygiene and dietary measures. Women performed SMBG (6times/day; fasting, before every meal, and after every meal), the results were gathered by the MyDiabby software or a phone call twice a week performed by a specialized nurse. They were provided specific glycemic targets: ≤0.92 g/l for fasting state, ≤ 1.20 g/l 2 hours after meals. Insulin therapy was initiated when glycemic objectives weren't achieved after 7 to 10 days of well-conducted hygienic-dietary rules, either with short-acting insulin analogues before meals and/or long-acting insulin analogues at bedtime. The obstetrician follow-up was consistent with the French guidelines (CNGOF).

Age, body mass index (BMI, defined as weight in kilograms divided by the square of height in meters), previous pregnancies, and risk factors were collected from electronic and paper hospital records. We collected only pre-gestational age and BMI.

For patients with GDM, we collected the date of GDM diagnosis, type of screening and plasma glucose values (fasting or OGTT), treatment start date, type of treatment (diet or insulin therapy), initial and final insulin dose expressed as a function of weight. HbA1c measurement was done at the first consultation with the diabetologist. HbA1c was measured using automated high-pressure liquid chromatography. It is managed by an automat of Capillarys Tera, Sebia. There is some uncertainty below HbA1C <3%. The Certified Quality Engineer has been given by Bio-Rad.

Regarding obstetric complications, delivery term, start of work mode (spontaneous or triggering), type of delivery (vaginal or caesarean) and shoulder dystocia were collected.
After delivery, infants received current routine care. Medical records were abstracted to obtain newborn's information. Sex and birth weight (in kilograms) were assessed at birth.

Pregnancy outcomes of interest were macrosomia defined as birth weight greater than or equal to 4000g, and " Large for gestational Age (LGA) to 90^{th} percentile according to the AUDIPOG formula which includes the term, sex and birth weight (Fig. 1) (12). Small for gestational age (SGA) was defined as gestational age-specific birth weight $<10^{th}$ centile according to the GARDOSI formula (Fig. 2) (13). Preterm delivery was determined as delivery prior to 37 weeks of gestation. Preeclampsia was defined as new-onset or worsening arterial hypertension after 20 weeks of gestation and the coexistence of one or more of the following new-onset conditions: proteinuria, other maternal organ dysfunction, or fetal growth restriction defined by the International Society for the study of Hypertension in Pregnancy (17).

Other neonatal complications assessed were Apgar score at 1 and 5 min, hospitalization in the neonatal unit and umbilical cord blood gas analysis. Neonatal intensive care unit admission was distinguished between respiratory distress syndrome, IUGR, or other grounds for transfer. Abnormal Apgar score at 1 and 5 minutes were defined as a score lower than 7 and arterial pH lower than 7.15.

We defined a composite criterion defined by the presence of at least one of the six following complications: Large for gestational Age, Small for gestational Age, preeclampsia, preterm delivery, transfer in neonatal intensive care unit and shoulder dystocia.

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

We assessed the association of HbA1c with pregnancy outcomes (all binary) using logistic regression models before and after adjustment in predefined risk factors of GDMs (age, BMI, family history of diabetes, personal history of GDM, personal history of macrosomia). We firstly examined the associations considering HbA1c as categorical variables using five pre-specified HbA1c classes: ≤4.5%, 4.6-4.9%, 5-5.5%, 5.6-5.9% and >5.9%, and secondly by considering as continuous variable. The results were expressed in odds ratios (OR) and their 95% confidence intervals (CI), calculated using HbA1c ≤ 4.5% as reference or calculated per 0.1% increase in HbA1c. Statistical testing was done at the two-tailed α level of 0.05.

RESULTS

This observational cohort study based on a total of 4384 women with gestational diabetes and at least one risk factor. In our cohort 2004 women were diagnosed before 20 weeks of gestation (early GDM) and 2253 after 20 weeks of gestation (late GDM).

Baseline maternal characteristics

Clinical characteristics of women are presented in Table 1. The subjects were 31.9 +/- 5.4 years old; their pregestational BMI was 28.4 +/- 6.4 kg/m^2. 52.9% of them reported family history of diabetes, 23% personal history of GDM and 13.5% personal history of macrosomia. 54.2% of GDM were diagnosed by fasting plasma glucose at a median time of 11.1 +/- 6.3 weeks defined as “early GDM” and 45.8 % were diagnosed by OGTT at a median time of 26.8+/- 2.9 weeks defined as “late GDM”. In the whole population, HbA1c was measured at a median time of 25 +/- 7.5 weeks gestation. Mean baseline HbA1c was 5.2 +/- 0.4%. HbA1c was measured at a median of 19.2 +/-6.4 weeks gestation in early GDM and 30.2 +/- 3.2 weeks gestation in late GDM. Mean baseline HbA1c was 5.1% +/-0.4 for women with early GDM and 5.2% +/- 0.4 for women with late GDM.

33 % of patients were treated with insulin. Treatment was introduced at a median of 26.9 +/- 7.2 weeks gestation and for a period of 14.1 +/- 7.6 weeks gestation.

Frequencies of obstetrical and neonatal outcomes are shown in Table 2. Gestational age at delivery was 39.1 +/- 1.6 weeks. There was 5.1% of preterm delivery. Cesarean section was performed in 22,2% of the population. 26.2% of patients needed to induce labor and instrumental extraction was required in 16.1%. Shoulder dystocia was found in 2.4%. The average birth-weight was 3410 +/- 532 g. The rate of macrosomia was 11.9% and the rate of LGA was 17.3%. The rate of SGA was 19.3%. Admission in the neonatal unit was required in

2.6% of newborn (respiratory distress syndrome 0.7%, IUGR 0.5%, and other grounds for transfer 1.3%). 41.6% of women had at least one complication of the composite criterion (LGA, preterm delivery, preeclampsia, SGA, shoulder dystocia and transfer in neonatal intensive care unit).

HbA1c and pregnancy outcomes

Women participating in this study were stratified in 5 groups according to the HbA1c value (≤4.5%; 4.6-4.9%; 5-5.5%; 5.6-5.9; >5.9%). We compared HbA1c classes with the lowest or referent category of ≤ 4.5%. In the class, the distribution of the number of GDM risk factors in each group of HbA1c is different. We notice that their number increased with HbA1c. Indeed, the frequency of one single risk factor was 47.1% in the lowest category of HbA1c (≤4.5%) to 24.7% in the highest (>5.9%). By contrast, no pregnant patient had five risk factor in the lowest category while they were 2.7% in the highest (≤4.5%: 0%; 4.6-4.9%: 0.3%; 5-5.5%: 1.2%; 5.6-5.9: 1.8%; >5.9%: 2.7%).

Adverse pregnancy outcomes stratified by HBA1c group are shown in Table 3. We compared the occurrence of each outcome between five HbA1c groups then treating HbA1c as continuous variables with odds-ratios calculated per 0.1% increase in HbA1c. Our results were provided without and, with adjustment for predefined risk factors of GDM.

There was a clear positive association between increasing baseline HbA1c and LGA, cesarean section and preterm delivery. While comparing between the five groups, higher levels of maternal HbA1c were significantly associated with increased frequency of LGA, preterm delivery, and cesarean ($p<0.001$ for all). An HbA1c threshold ≥5.6% was associated with a 2.12-fold (CI 1.29 to 3.46) and 1.64-fold (CI 1.06 to 2.53) increased risk of LGA and cesarean, respectively, compared to the group <4.5%. A baseline HbA1c >5.9% increased

risk of preterm delivery of 3.33 (CI 1.27 to 8.71). This significant association for HbA1c and LGA ($p<0.001$), cesarean ($p=0.006$) and preterm delivery ($p<0.001$) remained even after adjustment. It was observed, that a 0.1% increase in HbA1c, was associated with 1.06 times higher odds of LGA (CI 1.03 to 1.08), 1.03 times higher odds of cesarean (CI 1.01 to 1.05) and 1.07 times higher odds of preterm delivery (CI 1.04 to 1.11). Analyzing the different classes, we confirmed that a baseline HbA1c threshold ≥ 5.6% increased the risk of LGA (OR 1.87 (CI 1.13 to 3.12) and a threshold >5.9% increased the risk of preterm delivery (OR 3.09 (CI 1.18 to 8.11).

Shoulder dystocia was statistically significant after adjustment when HbA1c was considering as a continuous variable ($p=0.004$). 0.1% increase in HbA1c was associated with 1.08 times higher odds of shoulder dystocia (CI 1.02 to 1.13). However, this association was not found for comparison between five HbA1c groups ($p=0.12$ and $P=16$ after adjustment).

Preeclampsia was significantly when we compared HbA1c between the five groups ($p=0.02$) but not when HbA1c was considering as a continuous variable ($p=0.14$ and $p=0.19$ after adjustment).

SGA was significantly associated with HbA1c ($p=0.02$). However conversely the lowest prevalence of SGA was seen in those with the highest baseline HbA1c and appears to be a protective factor for SGA (OR 0.98 (CI 0.96 to 1.00). But it was not significant after adjustment.

Regarding neonatal outcomes (pH arterial, lower Apgar score at 1 and 5 min, and transfer in intensive care unit), no significant differences were observed in both analyses. After adjustment, results were similar.

Last, the table 3 demonstrated a statistically significant increased risk for the composite criterion ($p<0.001$). A baseline HbA1c between 5.6% and 5.9% was related to a 1.62-fold (CI 1.13 to 2.33) increased risk of presenting at least one complication: LGA, SGA, preeclampsia, preterm delivery, transfer in neonatal intensive care unit and shoulder dystocia. HbA1c remained statistically significant even after adjustment ($p<0.0001$).

All these analyses were carried out in both early GDM (2004 women diagnosed before 20 weeks of gestation) and late GDM (2253 women diagnosed after 20 weeks of gestation), with similar results.

CONCLUSIONS

In this large cohort of women with GDM, we found that a baseline HbA1c ≥5.6% predict an increased risk of several adverse pregnancy outcomes including LGA, SGA, preeclampsia, preterm delivery, transfer in neonatal intensive care unit and shoulder dystocia. More precisely, an HbA1c threshold ≥5.6% was significantly correlated with increased risk of LGA and cesarean compared to the group HbA1c <4.5%. An HbA1c > 5.9% was associated with increased risk of the preterm delivery. The effect of HbA1c was not affected by the term GDM diagnosis. Overall, our data support the use of a baseline HbA1c measurement could be useful to predict maternofoetal complications and to help clinicians to give the appropriate management.

Screening tests are chosen for their high sensitivity, which can be associated with a low specificity with a high number of false positive tests. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study showed that 50% of GDM according to the IADPSG criteria were made on plasma glucose measurements 1 and/or 2 hours after OGTT, fasting plasma glucose measurement being normal (3). Sensitivity of HbA1c level at 24-28 weeks of gestation is low to detect hyperglycemia in Pregnancy defined by IADPSG criteria: 5% for HbA1c ≥ 5.7% (39 mmol/mol) and 9% for HbA1c ≥ 5.9% (41 mmol/mol) (30) but it could be useful to predict adverse pregnancy outcomes. At this time, there is no international consensus for a threshold for GDM diagnosis and for the prediction of adverse event during pregnancy.

Our findings are in agreement with that of Sweeting *et al*. (32), who identified in a cohort of 2254 GDM that a higher baseline HbA1c was associated with increased risk of LGA (odds

ratio [95% IC] = 2.7 [1.5–4.9]), macrosomia (3.5 [1.4–8.6]), cesarean section (3.6 [2.1–6.2]), and hypertensive disorders (2.6 [1.1–5.8]) in standard GDM (≥24 weeks' gestation). In contrast to our results, we didn't find the same threshold > 5.9% in Sweeting's study and ≥5.6% in our study to predict adverse pregnancy outcome. In our study, we confirm that a baseline HbA1c between 5.6% and 5.9% was related to a 1.62-fold (CI 1.13 to 2.33) increased risk of presenting at least one materno-foetal complication. In the present study, the screening of GDM was based on risk factors contrary to sweeting's study all women undergoing universal screening. The diagnostic criteria are different: IADPSG criteria in our study and The Australian Diabetes in Pregnancy diagnostic criteria in Sweeting's study. Concerning materno-foetal complications, in contrast to our result, HbA1c was not significantly associated with increased risk of preterm delivery in Sweeting's study.

In our study, we didn't confirm that there was an association of SGA with the lowest baseline HBA1c category neither in early GDM neither in late GDM. Theses difference could be explained by the fact that there is a higher rate of women with insulin therapy in Sweeting's study (64.8% in the early GDM group, 45.9% in the standard GDM group and, 33% in our study). These differences can be explained by the characteristics of the population. We can speculate that we can find a higher rate of women with "overt diabetes" in the early GDM group in the Sweeting's study compared to our study.

Ye and al. (30) find the associations between HbA1c and preterm delivery, neonatal hyperbilirubinemia and neonatal asphyxia after adjustments for confounders in a retrospective study of 1959 women (1546 women without GDM and 413 with GDM). In our study, we didn't find any association with lower Apgar score at 1 and 5 minutes or intensive care unit admission contrary to Ye and al. This fact could be explained by the fact that our

population is a group of women with GDM and all of them have been treated. In our study, we confirm the association of HbA1c with preterm delivery even after adjustment with a threshold of 5.9%, contrary to Sweeting's study (32). Our results are in agreement with those of Yi-Ran Ho and al. (37) who confirm a higher rate of preterm delivery and macrosomia in a population of 1989 women with GDM. It could be interesting to know the prevalence of hydramnios to explain the relationship between the higher rate of preterm delivery and HbA1c according to the rate of LGA (38). We didn't report this variable in our study.

In our study, we didn't find any differences between early GDM group and late GDM group for the association HbA1c and maternofoetal complications. The results were similar in the 2 groups. Hughes et al. (28) identified in early GDM that an HbA1c threshold ≥5.9% was predictive of adverse pregnancy outcomes. Indeed it increased the risk of preeclampsia, shoulder dystocia, perinatal death, preterm delivery, induction of labor, LGA and major congenital abnormality. However, in this study, HbA1c testing was performed early during pregnancy (median of 47 days of gestation) and 5.9% HbA1c threshold was in favor of preexisting diabetes. They confirmed that women with HbA1c of 5.9% and 6.4% had poorer pregnancy outcomes than those with HbA1c <5.9% with a higher relative risk of major congenital anomaly and perinatal death. In the Sweeting's study (32). HbA1c testing was performed at 17.6 weeks of gestation with a higher rate of women with insulin therapy (64.8%). Otherwise, the definitions of early and late GDM group are different (before and after 20 week's gestation as it was proposed by McIntyre et al. (39).

Several studies argue that GDM obese patients have a higher risk of pregnancy outcomes than lean women (40- 42). In a Swiss study, the risk for cesarean section and LGA was twice higher when HbA1c was ≥5.5% and pre-pregnancy BMI ≥25 kg/m2 compared to women with

a BMI of < 25 kg/m2 and an HbA1c < 5.5% (40). Indeed, pre-pregnancy BMI and GWG were significantly correlated with the need for cesarean section, preterm delivery, pregnancy hypertension, LGA and macrosomia. In the HAPO study (42) the odds ratio for birth weight >90th percentile when patients presented only GDM was 2.19 (1.93–2.47), compared to 1.73 (1.50–2.00) in obese- non GDM patients, and 3.62 (3.04–4.32) for those who presented both GDM and obesity. Results for primary cesarean delivery and preeclampsia were similar. This illustrates the fact that both maternal GDM and obesity are independently associated with adverse pregnancy outcomes and their combination has a greater impact than either one alone. HbA1c remained significant for composite criterion even after risk factor adjustment ($p<0.0001$). In our study, model adjustments were risk factor of GDM contrary to Sweeting's study (32) where the confounding factors were age, ethnicity, prepregnancy BMI, and hypertensive disorders of pregnancy.

Our study has several strengths, which include a large sample size, detailed information regarding study population in particular the fact that it is a population of GDM women with risk factors. We have chosen to exclude in this cohort women with GDM without risk factors. All the women were followed by the same diabetologist or obstetrical staff. The type of intervention was standardized. Furthemore, the single laboratory measuring HbA1c provide for a robust investigational data set. However, some potential limitations require discussion. First, we did not know the hemoglobin and Mean Corpuscular Volume (MCV) levels in our patient, 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 (43). Furthermore, we were unable to compare these results with a population without GDM and, following the lack of reevaluations, the effect of insulin therapy was not

taken into account. The relations between HbA1c and risk of outcomes may be modified by the control of hyperglycemia because all women were treated during pregnancy. As indicated by previous studies, glucose control in GDM can significantly reduce the development of adverse pregnancy outcomes (44).

In summary, an HbA1c threshold ≥5.6% seems to identify women with a greater need of surveillance for LGA, and a threshold >5.9% seems to be associated with a higher risk of preterm delivery. Our finding suggests that an HbA1c measurement at diagnosis in GDM patients presenting risk factor may be a useful pragmatic guide for identifying women at risk for adverse outcomes including LGA, SGA, preeclampsia, preterm delivery, transfer in neonatal intensive care unit and shoulder dystocia. These clinical approaches can dichotomize GDM into high- and low-risk models of care at diagnostic. Regarding the resource constraints, it is important to us to propose new strategies in order to optimize care for patients with GDM. HbA1c measurement seems to be especially appropriate to detect high-risk women early in pregnancy compared with the many drawbacks of OGTT.

More recently, due to the COVID 19 pandemic, The Royal College of Obstetricians and Gynecologists recently reported unpublished data about the performances of HbA1c alone or in combination with FPG measurement to diagnose hyperglycemia in pregnancy in two studies (45). A combined approach with HbA1c and fasting plasma glucose could be useful first to detect hyperglycemia in pregnancy and to determine the population with the higher risk of materno-foetal complications.

ANNEXES

Fig 1. Birth Weight Percentiles for Gestational Age according to the AUDIPOG formula, which includes the term, sex and birth weight (12)

Fig 2. Birth Weight Percentiles for Gestational Age according to the AUDIPOG formula (13)

Table 1: Maternal Characteristics at the first day hospital consultation and Insulin Requirements

BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus; OGTT: Oral Glucose Tolerance Test.

Table 2: Pregnancy outcomes

Small for gestational age (GARDOSI) <10th centile; LGA (AUDIPOG) >90th centile.

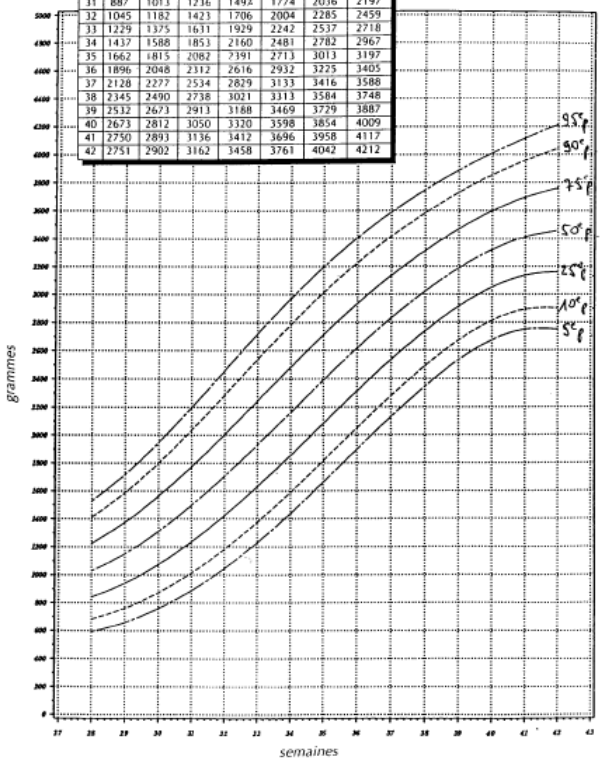
Table 3: Association of HbA1c with pregnancy outcomes

Small for gestational age (GARDOSI) <10th centile; LGA (AUDIPOG) >90th centile.

Fig. 1

Percentiles de poids (5° 10° 25° 50° 75° 90° 95°)

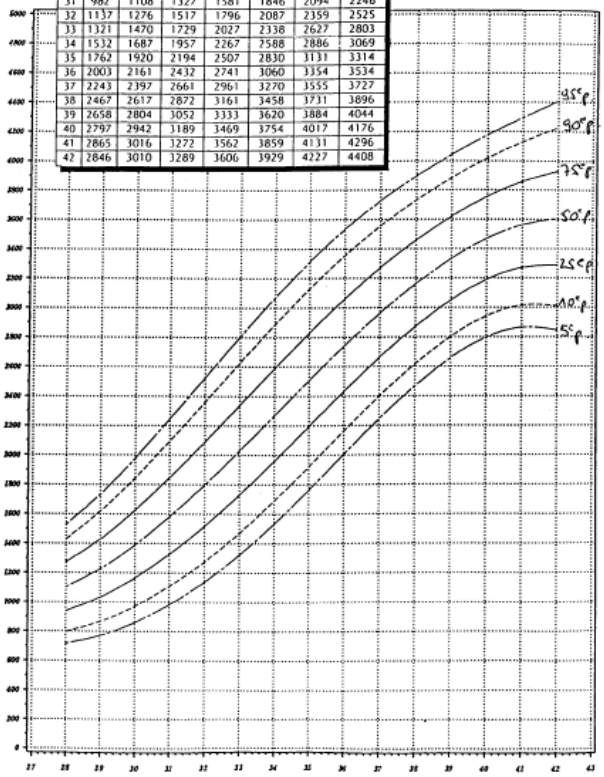
28	593	682	840	1027	1225	1413	1529
29	660	761	940	1151	1375	1588	1719
30	759	872	1073	1310	1561	1799	1946
31	887	1013	1236	1492	1774	2036	2197
32	1045	1182	1423	1706	2004	2285	2459
33	1229	1375	1631	1929	2242	2537	2718
34	1437	1588	1853	2160	2481	2782	2967
35	1662	1815	2082	2391	2713	3013	3197
36	1896	2048	2312	2616	2932	3225	3405
37	2128	2277	2534	2829	3133	3416	3588
38	2345	2490	2738	3021	3313	3584	3748
39	2532	2673	2913	3188	3469	3729	3887
40	2673	2812	3050	3320	3598	3854	4009
41	2750	2893	3136	3412	3696	3958	4117
42	2751	2902	3162	3458	3761	4042	4212



2 Courbe de croissance du P.N. des filles en fonction de l'âge gestationnel établie à partir des données de l'AUDIPOG.

Percentiles de poids (5° 10° 25° 50° 75° 90° 95°)

28	716	798	939	1103	1272	1431	1528
29	770	866	1033	1227	1429	1618	1733
30	859	971	1164	1389	1624	1843	1978
31	982	1108	1327	1581	1846	2094	2246
32	1137	1276	1517	1796	2087	2359	2525
33	1321	1470	1729	2027	2338	2627	2803
34	1532	1687	1957	2267	2588	2886	3069
35	1762	1920	2194	2507	2830	3131	3314
36	2003	2161	2432	2741	3060	3354	3534
37	2243	2397	2661	2961	3270	3555	3727
38	2467	2617	2872	3161	3458	3731	3896
39	2658	2804	3052	3333	3620	3884	4044
40	2797	2942	3189	3469	3754	4017	4176
41	2865	3016	3272	3562	3859	4131	4296
42	2846	3010	3289	3606	3929	4227	4408



e 1 Courbe de croissance du P.N. des garçons en fonction de l'âge gestationnel établie à partir des données de l'AUDIPOG.

Fig. 2

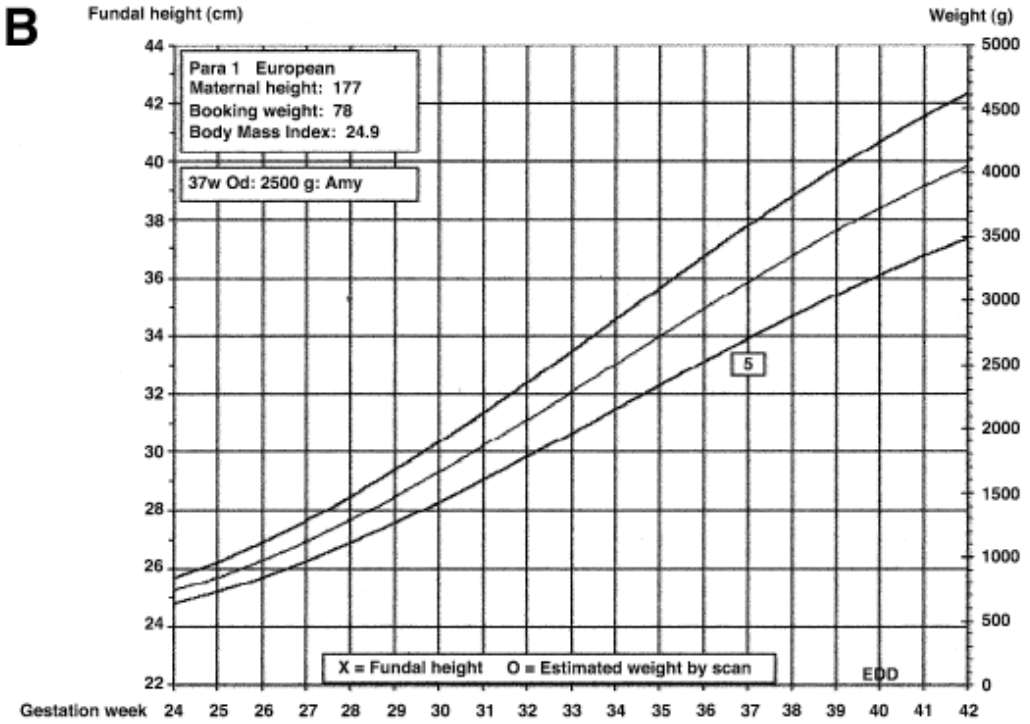


Table 1 Maternal Characteristics and metabolic data

Maternal Characteristics	N = 4383
Age, years	31.9 ± 5.4
Pregestational BMI, kg/m^2	28.4 ± 6.4
Multiparity	67.4%
Family history of diabetes	52.9%
Personal history of GDM	23%
Personal history of macrosomia	13.5%
Baseline HbA1c, %	5.2 ± 0.4
Gestation at GDM medical care, weeks	25 ± 7,5
GDM diagnosed by fasting plasma glucose	54.2%
Gestation at fasting plasma glucose, weeks	11.1 ± 6.3
Blood glucose value, g/l	1.0 (0.9 to 1.0)
GDM diagnosed by OGTT	45.8%
Gestation at OGTT, weeks	26.8 ± 2.9
OGTT values, g/l	
0 min	0.9 (0.9 to 1.0)
60 min	1.7 (1.4 to 1.9)
120 min	1.5 (1.2 to 1.6)
Insulin treatment	33%
Gestation insulin commenced, weeks	26.9 ± 7.2
Initial dose insulin, units/kg	0.1 (0.0 to 0.1)
Final dose insulin, units/kg	0.2 (0.1 to 0.4)
Duration of insulin treatment, weeks	14.1± 7.6

Values are %, mean ± SD or median (IQR)
SD : standard deviation , IQR : interquartile range

Table 2: Pregnancy outcomes		
Pregnancy outcomes	N = 4383	95% CI
Macrosomia	11.9%	10.9 to 12.9
LGA	17.3%	16.2 to 18.5
SGA	19.3%	18.1 to 20.5
Shoulder dystocia	2.4%	1.9 to 2.9
Preeclampsia	3.5%	3.0 to 4.1
Preterm delivery	5.1%	4.5 to 5.8
Caesarean	22.2%	20.9 to 23.4
Transfer in intensive care unit	2.6%	2.2 to 3.1
Abnormal Apgar score at 1 min <7	3.7%	3.2 to 4.3
Abnormal Apgar score at 5 min <7	0.9%	0.7 to 1.3
Arterial pH abnormality <7.15	15.9%	14.7 to 17.1

Values are % and their 95% confidence intervals (CI)
Abnormal Apgar score at 1 and 5 min <7/10