Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

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COVID-19 pandemic: Can fasting plasma glucose and HbA1c replace the oral glucose tolerance test to screen for hyperglycaemia in pregnancy?

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ARTICLE INFO

Article history:
Received 14 August 2020
Received in revised form
9 December 2020
Accepted 17 December 2020
Available online 13 January 2021

Keywords:
Collège National des Gynécologues Obstétriciens Français (CNGOF)
COVID-19
HbA1c
Oral glucose tolerance test
Société Francophone du Diabète (SFD)

ABSTRACT

Aims: To evaluate proposals considering HbA1c and fasting plasma glucose (FPG) measurement as a substitute for oral glucose tolerance test (OGTT) to diagnose hyperglycaemia in pregnancy (HIP) during COVID-19 pandemic.

Methods: Of the 7,334 women who underwent the OGTT between 22 and 30 weeks gestation, 966 had HIP (WHO diagnostic criteria, reference standard). The 467 women who had an available HbA1c were used for analysis. French-speaking Society of Diabetes (SFD) proposal to diagnose HIP during COVID-19 pandemic was retrospectively applied: HbA1c ≥5.7% (39 mmol/mol) and/or FPG level ≥5.1 mmol/l. SFD proposal sensitivity for HIP diagnosis and the occurrence of HIP-related events (preeclampsia, large for gestational age infant, shoulder dystocia or neonatal hypoglycaemia) in women with false negative (FN) and true positive (TP) HIP-diagnoses were evaluated.

Results: The sensitivity was 57% [95% confidence interval 52–62]. FN women had globally lower plasma glucose levels during OGTT, lower HbA1c and body mass index than those TP. The percentage of HIP-related events was similar in FN (who were cared) and TP cases,

Abbreviations: 1h-PG, plasma glucose value 1 hour after 75g oral glucose tolerance test; 2h-PG, plasma glucose value 2 hours after 75g oral glucose tolerance test; CNGOF, French National College of Obstetricians and Gynecologists (Collège National des Gynécologues et Obstétriciens Français); COVID-19, Coronarovirus Disease 19; DIP, diabetes in pregnancy; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HIP, hyperglycaemia in pregnancy; IADPSG, International Association of Diabetes Pregnancy Study Group; NICE, National Institute for Health and Care Excellence; OGTT, 75-g oral glucose tolerance test; SD, standard deviation; SFD, French-speaking Society of Diabetes (Société Francophone du Diabète); WG, weeks of gestation; WHO, World Health Organization

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https://doi.org/10.1016/j.diabres.2020.108640
0168-8227/

respectively 19.5 and 16.9% (p = 0.48). We observed similar results when women at high risk for HIP only were considered.
Conclusion: The SFD proposal has a poor sensitivity to detect HIP. Furthermore, it fails to have any advantages in predicting adverse outcomes.

1. Introduction

To slow the spread of Coronarovirus Disease 19 (COVID-19), it is critical to practice social distancing and to reduce contacts, including in phlebotomy centres. This is crucial regarding pregnant women and screening for hyperglycaemia in pregnancy (HIP). The oral glucose tolerance test (OGTT) - reference standard test- requires measurement of fasting (FPG), 1-hour (1h-PG), 2-hour (2h-PG) and sometimes 3-hour plasma glucose [1–6], time that the patient may spent waiting in the crowded phlebotomy centres. In this context, UK [7], France [8] and Japan [9] proposed to temporarily replace OGTT by FPG and HbA1c measurement. The rationale behind this proposal is to combine tests and to reduce the time spent in phlebotomy centres.

Such a proposal should be balanced by the need to provide appropriate care to ensure the best possible pregnancy outcomes for women and their infants. Therefore, screening procedures based on FPG and HbA1c measurement should be sensitive enough to diagnose most of the women with HIP. As a matter of fact, not looking for HIP might lead to a doubling of the rate of events during pregnancy [10,11]. However, missing a few HIP diagnoses could be less deleterious than expected if the false negative cases were at lower risk of HIP-related adverse events than the true positive ones.

The aim of the study was to retrospectively evaluate in a large cohort of women with HIP [12,13] *(i)* the sensitivity of the French-speaking Society of Diabetes (SFD: Société Francophone du Diabète) / French National College of Obstetricians and Gynecologists (CNGOF: Collège National des Gynécologues et Obstétriciens Français) temporary COVID-19 proposal for HIP diagnosis and *(ii)* the occurrence of HIP-related events in false negative and true positive cases of HIP when applying this proposal.

2. Material and methods

2.1. Data collection

We have conducted this observational study in our University hospital in a suburban area of Paris, Bondy, France, where medical electronic records of maternal and neonatal events at birth have been routinely collected between January 2012 and October 2016 [12,13]. In addition, data on HIP screening were available for all women. Women were informed that their medical records could be used for research, unless they opposed [12,13]. We analyzed the data anonymously. Our database was declared to the French Committee for computerized data (CNIL: Commission Nationale de l'Informatique et des Libertés, number 1704392v0).

2.2. Screening for and management of hyperglycaemia in pregnancy

In our centre, we have been following the French recommendations for HIP screening, except that our policy is to universally screen every woman, both at the beginning of pregnancy and after 24 weeks of gestation (WG) if prior screening was normal or not done. Early screening during pregnancy is based on FPG measurement. Women with FPG level $\geq$5.1 mmol/L are diagnosed with HIP and immediately managed appropriately [3]. Those without early-diagnosed HIP are planned to undergo a 75 g OGTT between 24 and 28 WG, with measurement of FPG, 1h-PG and 2h-PG [3]. International Association of Diabetes Pregnancy Study Group (IADPSG) [1] / World Health Organization (WHO) [2] criteria are used for HIP diagnosis, as they have been endorsed in France [3]. Accordingly, gestational diabetes mellitus (GDM) is defined by FPG 5.1–6.9 mmol/L and/or 1h-PG $\geq$10.0 mmol/L and/or 2h-PG 8.5–11.0 mmol/L during OGTT, whereas diabetes in pregnancy (DIP) is defined by FPG $\geq$7.0 and/or 2h-PG value $\geq$11.1 mmol/L [3].

After HIP diagnosis, all women are referred to our multidisciplinary team including a diabetologist, an obstetrician, a midwife, a dietician and a nurse educator and are managed according to French recommendations. They receive individualized dietary advice, education for performing self-monitoring of blood glucose levels six times per day and visit the diabetologist every 2–4 weeks. At the beginning of this educational program, HbA1c level is centrally measured in our hospital (turbidimetric inhibition immunoassay for the in vitro determination of hemoglobin A1c and total hemoglobin in whole blood; Cobas 6000; Roche). Insulin treatment is initiated when pre-prandial or 2-hour post-prandial glucose levels are respectively above 5.0 or 6.7 mmol/L during follow up, according to the French guidelines [3]. Obstetrical care also is also managed according to the French recommendations [3].

2.3. Reference standards and selection criteria

Inclusion criteria were age 18–50 years, singleton pregnancies, no personal history of either diabetes or bariatric surgery, no early HIP during this current pregnancy, OGTT performed between 22 and 30 WG.

We then selected among the women who had HIP according to IADPSG/WHO criteria (as described earlier in the article;

reference standard) those who had an HbA1c level measurement (additional Fig. 1).

2.4. *Description of tested algorithm*

According to SFD/CNGOF COVID-19 proposal [8], no OGTT is performed and women with either HbA1c ≥5.7% (39 mmol/mol) or FPG ≥5.1 mmol/l are diagnosed with HIP.

We then explored whether the results would be similar if selective screening would be applied, which is recommended by SFD/CNGOF proposal. For this sensitivity analysis, we only selected the women who had any of the following risk factors (reference standard in case of selective screening): body mass index ≥25 kg/m^2; age ≥35 years; first-degree relative with history of diabetes; previous pregnancy with HIP or with macrosomic infant [3].

2.5. *HIP-related events*

The main predefined endpoint was the occurrence of a HIP-related event. This composite criterion included at least one of the following events: *(i)* preeclampsia (blood pressure ≥140/90 mmHg on two recordings four hours apart and proteinuria at or above 300 mg/24 h or 3+ on dipstick testing in a random urine sample), *(ii)* large-for-gestational-age infant (birth weight greater than the 90th percentile for a standard French population [12,13]), *(iii)* shoulder dystocia defined as the use of obstetrical manoeuvers (McRoberts manoeuver, episiotomy after delivery of the foetal head, suprapubic pressure, posterior arm rotation to an oblique angle, rotation of the infant by 180 degrees, or delivery of the posterior arm) and neonatal hypoglycaemia, defined as at least one blood glucose value below 2.2 mmol/L during the first two days of life [12,13]. We also considered each one of the previous events separately, the need for insulin during pregnancy, a preterm delivery (delivery before 37 completed weeks) and admission to a neonatal intensive care unit.

2.6. *Statistics*

Baseline continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as frequencies (percentages). To explore the presence of any selection bias, the baseline characteristics of the women who were included were compared to those who were not. To compare continuous variables ANOVA and Chi-squared (X^2) test or Fisher-exact test for categorical variables were used. The reference standard was the results of OGTT according IADPSG/WHO criteria. The sensitivity of the COVID-19 proposal for HIP diagnosis was evaluated.

A sensitivity analysis by restricting inclusion to women at high-risk for HIP, as SFD/CNGOF recommend selective screening [7,8], was also made. Finally, another sensitivity analysis considering the same statistical analyses only in women with HbA1c measured within four (and not six) weeks after OGTT was also made.

The sensitivities by using different thresholds of FPG or HbA1c to diagnose HIP were also evaluated.

Finally, characteristics and event rates of true positive and false negative HIP diagnoses applying SFD/CNGOF proposal were compared. Student *t* test or the Mann Whitney test for Gaussian or non-Gaussian continuous variables respectively were used, and chi-squared (X^2) test or the Fisher-exact tests for categorical variables.

All tests were two-sided and used a significance level of p value at 0.05. Analyses were conducted using and R 3.6.3 software (www.r-project.org).

3. Results

3.1. *Population characteristics*

As shown in the flow chart (Additional Fig. 1), 467 women were included, and their characteristics are described in Table 1.

The baseline characteristics of these included women and the non-included women were compared with the ones of the 88 women who had HbA1c measured >6 weeks after the OGTT and the 441 who had no HbA1c measured (additional Table 1). Globally, the highest 1h-PG and 2h-PG levels during diagnostic OGTT was observed in the study population. HbA1c level was higher in the women who had HbA1c measured greater than 6 weeks after OGTT (non-included women) than in those for whom HbA1c was measured within 6 weeks. The included women were also slightly older and were more prone to have had hyperglycaemia in previous pregnancy.

For sensitivity analyses, 397 women with risk factors (selective screening) were included. Table 2 shows the characteristics of these women.

3.2. *Sensitivity of SFD-CNGOF COVID-19 proposal to diagnose HIP cases*

Using universal screening, SFD-CNGOF COVID-19 proposal would have identified 266/467 women with HIP (sensitivity 57% [95% confidence interval 52–62]). Out of the 32 women having DIP according to OGTT (reference standard), 9 women would have been classified as not having HIP, 18 women with GDM and 5 women with DIP.

Using selective screening (sensitivity analysis), SFD-CNGOF COVID-19 proposal would have identified 232/397 women with HIP (sensitivity 58% [95% confidence interval 53–64]). Out of the 30 women having DIP according to OGTT, 8 women would have been classified as not having HIP, 17 women with GDM and 5 women with DIP.

Additional Table 2 shows *(i)* the sensitivity of HbA1c ≥5.7% (39 mmol/mol) (15% [95% confidence interval 12–19]) or FPG ≥5.1 mmol/l alone (54% [95% confidence interval 50–59]) for HIP diagnosis and *(ii)* that the results were globally similar when only women for whom HbA1c was measured within 4 weeks after OGTT were considered (sensitivity analysis).

3.3. *Sensitivities applying different thresholds of FPG or HbA1c to diagnose HIP cases*

Tables 3 and 4 show to what extent applying lower thresholds of FPG (Table 3) or HbA1c (Table 4) would increase the sensitivities of SFD/CNGOF COVID-19 proposal to diagnose HIP cases.

Table 1 – Characteristics of the women by true positive and false negative HIP diagnoses applying universal screening.

	Total n = 467	True positive diagnoses n = 266	False negative diagnoses n = 201	p
OGTT between 22 and 30 WG				
Fasting plasma glucose (mmol/L)	5.1 (0.6)	5.5 (0.5)	4.5 (0.4)	<0.001
Fasting plasma glucose ≥ 5.1 mmol/L	254 (54.4)	254 (95.5)	0 (0.0)	<0.001
1-hour plasma glucose (mmol/L)	9.6 (1.9)	9.3 (2.2)	10.1 (1.3)	<0.001
2-hour plasma glucose (mmol/L)	8.4 (1.9)	8.1 (2.2)	8.8 (1.3)	<0.001
Gestational age when OGTT (WG)	26.2 (1.9)	26.1 (1.9)	26.3 (1.9)	0.46
HbA1c (%)	5.2 (0.5)	5.3 (0.5)	5.0 (0.4)	<0.001
HbA1c (mmol/mol)	33 (6)	34 (6)	31 (4)	<0.001
HbA1c ≥ 5.7% (39 mmol/mol)	70 (15)	70 (26.3)	0 (0.0)	<0.001
Gestational age when HbA1c (WG)	29.3 (2.4)	29.2 (2.3)	29.4 (2.4)	0.35
Glycaemic status (reference standard: IADPSG/WHO criteria)				0.08
GDM	435 (93.1)	243 (91.4)	192 (95.5)	
DIP	32 (6.9)	23 (8.6)	9 (4.5)	
Characteristics				
Age (years)	33.2 (5.4)	33.2 (5.4)	33.0 (5.5)	0.70
Preconception body mass index (kg/m^2)	26.8 (5.8)	27.6 (6.1)	25.8 (5.1)	0.001
Preconception hypertension	9 (1.9)	5 (1.9)	4 (2.0)	1
Family history of diabetes	139 (29.8)	82 (30.8)	57 (28.5)	0.56
Employment	201 (43.2)	118 (44.7)	83 (41.5)	0.46
Smoking before pregnancy	37 (7.9)	23 (8.6)	14 (7.0)	0.51
Parity (n)	2.3 (1.2)	2.3 (1.2)	2.2 (1.2)	0.30
Previous pregnancy(ies)				
History of hyperglycaemia in pregnancy				0.83*
First child	145 (31.0)	72 (27.1)	73 (36.3)	
No	243 (52.0)	148 (55.6)	95 (47.3)	
Yes	79 (16.9)	46 (17.3)	33 (16.4)	
History of macrosomia				0.12*
First child	145 (31.0)	72 (27.1)	73 (36.3)	
No	298 (63.8)	176 (66.2)	122 (60.7)	
Yes	24 (5.1)	18 (6.8)	6 (3.0)	
History of hypertensive disorders				0.72*
First pregnancy	105 (22.5)	50 (18.8)	55 (27.4)	
No	344 (73.7)	205 (77.1)	139 (69.2)	
Yes	18 (3.9)	11 (4.1)	7 (3.5)	
History of fetal death				0.20*
First pregnancy	105 (22.5)	50 (18.8)	55 (27.4)	
No	347 (74.3)	205 (77.1)	142 (70.6)	
Yes	15 (3.2)	11 (4.1)	4 (2.0)	
Ethnicity				0.053
North African	156 (33.5)	85 (32.2)	71 (35.3)	
European	103 (22.2)	55 (20.8)	48 (23.9)	
Sub-Saharan African	63 (13.5)	39 (14.8)	24 (11.9)	
Indian-Pakistan-Sri Lankan	79 (17.0)	50 (18.9)	29 (14.4)	
Caribbean	24 (5.2)	19 (7.2)	5 (2.5)	
Asian	19 (4.1)	8 (3.0)	11 (5.5)	
Other	21 (4.5)	8 (3.0)	13 (6.5)	
Events during pregnancy				
HIP-related event	86 (18.4)	52 (19.5)	34 (16.9)	0.47
Preeclampsia	19 (4.1)	9 (3.4)	10 (5.0)	0.38
Large for gestational age infant	56 (12.0)	36 (13.5)	20 (10.0)	0.24
Shoulder dystocia	0	0	0	
Neonatal hypoglycaemia	14 (3.0)	8 (3.0)	6 (3.0)	0.99
Preterm delivery	42 (9.0)	25 (9.4)	17 (8.5)	0.72
Offspring hospitalization	116 (24.9)	75 (28.2)	41 (20.6)	0.06
Insulin therapy during pregnancy	252 (54.0)	168 (63.2)	84 (41.8)	<0.001

Data are n (%) or mean (standard deviation).
DIP: diabetes in pregnancy; GDM: gestational diabetes mellitus; HIP: hyperglycaemia in pregnancy; OGTT: oral glucose tolerance test; WG: weeks of gestation.
HIP-related event is a composite endpoint: preeclampsia or LGA infant or shoulder dystocia or neonatal hypoglycaemia.
*Yes vs No.

Table 2 – Characteristics of the women by true positive and false negative HIP diagnoses applying selective screening (sensitivity analysis).

	Total n = 397	True positive diagnoses n = 232	False negative diagnoses n = 165	p
OGTT between 22 and 30 WG				
Fasting plasma glucose (mmol/L)	5.1 (0.6)	5.5 (0.5)	4.6 (0.4)	<0.001
Fasting plasma glucose ≥ 5.1 mmol/L	221 (55.7)	221 (95.3)	0 (0.0)	<0.001
1-hour plasma glucose (mmol/L)	9.8 (1.8)	9.5 (2.1)	10.2 (1.3)	<0.001
2-hour plasma glucose (mmol/L)	8.5 (1.9)	8.2 (2.3)	8.7 (1.3)	0.01
Gestational age when OGTT (WG)	26.2 (1.9)	26.1 (1.9)	26.3 (1.9)	0.41
HbA1c (%)	5.2 (0.5)	5.3 (0.5)	5.0 (0.4)	<0.001
HbA1c ≥ 5.7%(39 mmol/mol)	62 (15.6)	62 (26.7)	0 (0.0)	<0.001
HbA1c (mmol/mol)	33 (6)	35 (6)	31 (4)	<0.001
Gestational age when HbA1c (WG)	29.2 (2.3)	29.1 (2.3)	29.4 (2.4)	0.35
Glycemic status (Gold standard: IADPSG/WHO criteria)				0.09
GDM	367 (92.4)	210 (90.5)	157 (95.2)	
DIP	30 (7.6)	22 (9.5)	8 (4.8)	
Characteristics				
Age (years)	33.9 (5.3)	33.9 (5.3)	33.9 (5.5)	0.99
Preconception body mass index (kg/m^2)	27.7 (5.7)	28.4 (6.0)	26.7 (5.1)	0.003
Preconception hypertension	9 (2.3)	5 (2.2)	4 (2.4)	1
Family history of diabetes	139 (35.0)	82 (35.3)	57 (34.5)	0.87
Employment	180 (45.5)	108 (46.8)	72 (43.6)	0.54
Smoking before pregnancy	30 (7.6)	19 (8.2)	11 (6.7)	0.57
Parity	2.4 (1.2)	2.4 (1.2)	2.4 (1.3)	0.87
Previous pregnancy(ies)				
History of hyperglycaemia in pregnancy				0.93*
First child	106 (26.7)	57 (24.6)	49 (29.7)	
No	212 (53.4)	129 (55.6)	83 (50.3)	
Yes	79 (19.9)	46 (19.8)	33 (20.0)	
History of macrosomia				0.16*
First child	106 (26.7)	57 (24.6)	49 (29.7)	
No	267 (67.3)	157 (67.7)	110 (66.7)	
Yes	24 (6.0)	18 (7.8)	6 (3.6)	
History of hypertensive disorders				0.81*
First pregnancy	72 (18.1)	37 (15.9)	35 (21.2)	
No	307 (77.3)	184 (79.3)	123 (74.5)	
Yes	18 (4.5)	11 (4.7)	7 (4.2)	
History of fetal death				0.17*
First pregnancy	72 (18.1)	37 (15.9)	35 (21.2)	
No	312 (78.6)	185 (79.7)	127 (77.0)	
Yes	13 (3.3)	10 (4.3)	3 (1.8)	
Ethnicity				0.11
North African	141 (35.6)	78 (33.8)	63 (38.2)	
European	83 (21.0)	47 (20.3)	36 (21.8)	
Sub-Saharan African	52 (13.1)	33 (14.3)	19 (11.5)	
Indian-Pakistan-Sri Lankan	65 (16.4)	40 (17.3)	25 (15.2)	
Caribbean	23 (5.8)	19 (8.2)	4 (2.4)	
Asian	14 (3.5)	7 (3.0)	7 (4.2)	
Other	18 (4.5)	7 (3.0)	11 (6.7)	
Events during pregnancy				
HIP-related event	80 (20.2)	48 (20.7)	32 (19.4)	0.75
Preeclampsia	18 (4.5)	8 (3.4)	10 (6.1)	0.22
Large for gestational age infant	52 (13.1)	34 (14.7)	18 (10.9)	0.28
Shoulder dystocia	0	0	0	
Neonatal hypoglycaemia	12 (3.9)	7 (3.0)	6 (3.6)	0.73
Preterm delivery (<37 weeks)	40 (10.1)	24 (10.3)	16 (9.7)	0.83
Offspring hospitalization	99 (25.0)	63 (27.2)	36 (22.0)	0.24
Insulin therapy during pregnancy	223 (56.2)	150 (64.7)	73 (44.2)	<0.001

Data are n (%) or mean (standard deviation).
DIP: diabetes in pregnancy; GDM: gestational diabetes mellitus; HIP: hyperglycaemia in pregnancy; LGA: large for gestational age; OGTT: oral glucose tolerance test; WG: weeks of gestation.
HIP-related event is a composite endpoint: preeclampsia or LGA infant or shoulder dystocia or neonatal hypoglycaemia.
Selective screening according to SFD/CNGOF guidelines: body mass index ≥ 25 kg/m^2; age ≥ 35 years; first-degree relative with history of diabetes; previous pregnancy with HIP or with macrosomic infant.
*Yes vs No.

Table 3 – Sensitivity applying different thresholds of fasting plasma glucose, with constant HbA1c threshold, to diagnose cases of hyperglycaemia in pregnancy.

Fasting plasma glucose threshold, mmol/L	Sensitivity [95% confidence interval]
4.6	0.78 [0.74–0.82]
4.7	0.76 [0.72–0.80]
4.8	0.70 [0.66–0.74]
4.9	0.66 [0.61–0.70]
5.0	0.60 [0.56–0.65]
5.1	0.57 [0.52–0.62]

The threshold of HbA1c to diagnose hyperglycaemia in pregnancy is constant (≥5.7%, 39 mmol/mol), while the threshold of fasting plasma glucose value varies.

Table 4 – Sensitivity applying different thresholds of HbA1c, with constant fasting plasma glucose threshold, to diagnose cases of hyperglycaemia in pregnancy.

HbA1c threshold, % (mmol/mol)	Sensitivity [95% confidence interval]
5.0 (31)	0.80 [0.76–0.83]
5.1 (32)	0.76 [0.72–0.80]
5.2 (33)	0.70 [0.66–0.74]]
5.3 (34)	0.67 [0.63–0.71]
5.4 (36)	0.64 [0.60–0.68]
5.5 (37)	0.62 [0.57–0.66]
5.6 (38)	0.57 [0.54–0.63]
5.7 (39)	0.57 [0.52–0.62]

The threshold of fasting plasma glucose to diagnose hyperglycaemia in pregnancy is constant (≥5.1 mmol/L), while the threshold of HbA1c varies.

3.4. *Characteristics of true positive and false negative cases of HIP applying SFD-CNGOF COVID-19 proposal*

Table 1 shows the comparison of HIP true positive and false negative case subgroups with universal screening, while Table 2 shows the results with selective screening (sensitivity analysis). When universal or selective screening were used, lower FPG and HbA1c levels, as well as a lower mean body mass index; and higher 1h-PG and 2h-PG were found in the false negative case subgroup compared to the true positive case subgroup. The percentage of women who needed insulin therapy during pregnancy was also lower.

3.5. *Prognosis of true positive and false negative HIP case subgroups applying SFD-CNGOF COVID-19 proposal*

The percentage of HIP-related events was similar in true positive and false negative case subgroups of HIP considering universal (Table 1) or selective screening (Table 2). The percentage of each outcome was also similar in both groups in case of universal screening (Table 1). The results were similar when selective screening was used (Table 2, sensitivity analysis).

4. Discussion

OGTT is the cornerstone of the diagnosis of HIP. Besides its inconvenience and a high variability of 2h-PG [14], it is time-consuming and not appropriate for social distancing. The results show that the SFD/CNGOF proposal to substitute OGTT for HbA1c and FPG measurement in the context of COVID-19 pandemic has a poor sensitivity to detect HIP. Furthermore, screening based on HbA1c and FPG does not appear to select women with the highest rate of adverse events during pregnancy.

Several studies have explored the accuracy of FPG [19–21] and HbA1c measured between 24 and 28 GW for HIP diagnosis defined according to IADPSG/WHO criteria [22–25]. Like in our study, FPG measurement alone, with a threshold of 5.1 mmol/

L, was shown to be not highly sensitive [19–21,25–27]. For example, a recent study from UK reported that sensitivity of FPG 5.1 mmol/L or more was 63.8% [26]. Regarding the use of HbA1c, when HIP was defined with National Institute for Health and Care Excellence (NICE) criteria, HbA1c ≥6.0% (42 mmol/mol) was reported to have a sensitivity of 22% but lower thresholds of HbA1c were not tested [28]. HbA1c ≥5.7% (39 mmol/mol) was reported to have a sensitivity of 73.3% in India [23] but only 9% in China [22] to identify women with HIP according to IADPSG/WHO criteria. Overall, the sensitivity of an isolated HbA1c measurement with this threshold is therefore considered to be poor. This may be partially due to physiological changes that occur during pregnancy, including erythrocyte turnover, erythropoietin production and anaemia [15,29]. It has also been reported that HbA1c levels show some variations according to ethnic origin [30,31].

To compensate the lack of sensitivity when using FPG or HbA1c alone at current thresholds, some national societies proposed to associate both measurements to diagnose HIP [7–9]. We show here that this strategy has not a good sensitivity either (59%), as recently reported in Japan (39%) [9]. We found only one published study exploring whether associating both parameters was more sensitive than considering each parameter alone: the area under the curve to identify HIP (defined by Carpenter and Coutsan criteria after 100 g OGTT) of FPG, HbA1c and both of them were 0.833, 0.784 and 0.863, respectively [32].

Missing HIP diagnoses would be less deleterious than expected if women with false negative HIP diagnosis were at lower risk for HIP-related adverse events than women with a true positive diagnosis. This could have been expected as both high FPG and HbA1c [22,23,33] levels after 24 WG are associated with a poor prognosis. Interestingly, our results have shown that the prognosis of false negative and true positive cases was in fact similar. Considering that *(i)* all the women included in this study had HIP according to IADPSG/WHO criteria and were therefore managed for this condition and that *(ii)* not caring for HIP in low-risk women might lead to twice as much events during pregnancy [7,8], missing diagnosis for those women might be deleterious. As a matter of fact, in our study, more than 40% of women with false negative diagnoses received insulin therapy in addition to diet and physical activity counselling. The incidence of insulin requirement was also similar in true positive and false negative cases of HIP in the Japanese series [9]. A recently published study based on Hyperglycaemia and Adverse Pregnancy Outcome dataset [34] have evaluated the accuracy of FPG ≥5.6 mmol/L and/or HbA1c ≥5.7% (39 mmol/mol) to diagnose HIP, using the NICE guidance as reference Standard (FPG ≥5.6 mmol/L and/or 2-h plasma glucose ≥7.8 mmol/L) [35]. Women whose HIP would remain undetected post COVID-19 (missed HIPs) displayed similar rates of large-for-gestational-age infant, neonatal hypoglycaemia and preterm delivery, but a lower rate of pregnancy-related hypertension, to those with post COVID-19 HIP. To note, women in this study were untreated [34]. However, randomized studies are required to draw definite conclusions.

The strengths of our studies include the large number of subjects with HIP and a pragmatic guidance-based approach. The prospectively collected standardized data provide a robust investigational data set and they could apply selective (sensitivity analysis) or universal screening for reference Standard. Our evaluation was limited to women who underwent OGTT in the late second and early third trimester (22–30 WG). Finally, our study could compare not only characteristics but also prognosis of true positive and false negative cases of HIP. We however have to consider while interpreting the results that all included women were cared for HIP in our observational series.

Our study has limitations. Actually, HbA1c level was measured in our centre only in women with HIP according to IADPSG/WHO criteria. Therefore, sensitivity but not specificity, nor positive and negative predictive values of COVID-19 proposals could be investigated. Another issue could be that HbA1c was not measured at the same time as FPG. In pregnant women, the time course of HbA1c is actually biphasic with a decrease during the second trimester, a nadir at 24 WG and an increase during the last trimester [15–18]. This is the reason why women for whom HbA1c was measured more than 6 weeks after OGTT were not included. Indeed, these non-included women had higher HbA1c level than women who had their HbA1c measured within 6 weeks after the OGTT. Our sensitivity analysis showed that sensitivity was similar when women had their HbA1c measured either within 4 weeks or 6 weeks after OGTT. Finally, around one half of women with HIP had no HbA1c measured but their characteristics were globally similar as those of women who were included.

To conclude, due to their low sensitivities, even during current and future pandemics, we do not recommend the routine application of SFD/CNGOF current proposals, *i.e.* to use FPG and HbA1c measurement with proposed thresholds as a substitute for OGTT. This proposal should all the more be temporary and other options might be considered [36,37]. As shown in our study, considering lower FPG [21,25,32] and HbA1c thresholds [22–24] would increase sensitivity. However, it would also decrease specificity, which is an issue during pandemics. Indeed, it is critical to practice social distancing not only at OGTT testing centres but also within the health care setting -where false positive cases of HIP would be managed. Limiting the proportion of women addressed for OGTT according to FPG [27,36] and/or HbA1c level [22–24] might be better options. For example, FPG thresholds of ≤4.4 mmol/L have been reported to rule out HIP in 50–65% of women with a sensitivity of 80–95% [19–21]. Also, as suggested in the case of a personal history of bariatric surgery [38], women could self-monitor their blood glucose at home but this implies education to do so [37]. Thus, there is an urgent need to validate new methods to diagnose and manage HIP in order to be ready to face future pandemics/lockdowns.

Author contributions

C.N. prepare and made statistic, and wrote manuscript; S.P., S. T., H.B., M.S., N.B. and L.C. contributed to discussion, reviewed/edited manuscript; E.V. co-directed research and reviewed/edited manuscript; E.C. directed research and wrote manuscript.

Acknowledgements

Emmanuel Cosson and Lionel Carbillon are the guarantors of this work. The authors thank Lilly France for funding. The authors do not report any conflict of interest. Especially, apart funding, Lilly France did not participate in any part of this study. We thank Sylvie Picard, MD, PhD, Dijon, France, for her help in the preparation of the English manuscript and Didier André, AP-HP, Unité de Recherche Clinique GHU-SSPD, for data management. Finally, we thank Phuc Thu Trang Nguyen, AP-HP, Unité de Recherche Clinique St-Louis-Lariboisière, Université Denis Diderot, Paris, France for help in collecting HbA1c results.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108640.

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