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Research paper

Mental health and its associations with glucose-lowering medication in women with gestational diabetes mellitus. A prospective clinical cohort study

Leah Gilbert [a,*], Argyro Nikolaou [b], Dan Yedu Quansah [a], Jean-Benoît Rossel [c], Antje Horsch [d,e,1], Jardena J. Puder [a,*,1]

[a] Obstetric Service, Woman-Mother-Child Department, Lausanne University Hospital, Avenue Pierre-Decker 2, 1011 Lausanne, Switzerland
[b] Clinical Pharmacology and Toxicology Division, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, Geneva, Switzerland
[c] Clinical Trials Unit, University of Bern, Mittelstrasse 43, 3012 Bern, Switzerland
[d] Institute of Higher Education and Research in Healthcare (IUFRS), University of Lausanne, Route de la Corniche 10, 1010 Lausanne, Switzerland
[e] Neonatology Service, Woman-Mother-Child Department, Lausanne University Hospital, Avenue Pierre-Decker 2, 1011 Lausanne, Switzerland

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ABSTRACT

Aims: Mental health symptoms are frequent in women with gestational diabetes mellitus (GDM) and may influence glycemic control. We therefore investigated if mental health symptoms (high depression and low well-being scores) predicted a need for glucose-lowering medication and if this use of medication influenced the trajectory of mental health during pregnancy and in the postpartum period.

Methods: We included 341 pregnant women from a cohort of GDM women in a Swiss University Hospital. The World Health Organization Well-being Index-Five was collected at the first and last GDM and at the postpartum clinical visits and the Edinburgh Postnatal Depression Scale at the first GDM and the postpartum clinical visits. Medication intake was extracted from participants' medical records. We conducted linear and logistic regressions with depression as an interaction factor.

Results: Mental health symptoms did not predict a need for medication (all $p \geq 0.29$). Mental health improved over time (both $p \leq 0.001$) and use of medication did not predict this change (all $p \geq 0.40$). In women with symptoms of depression, medication was associated with less improvement in well-being at the postpartum clinical visit (p for interaction=0.013).

Conclusions: Mental health and glucose-lowering medication did not influence each other in an unfavourable way in this cohort of women with GDM.

1. Introduction

Gestational diabetes mellitus (GDM) is defined as a glucose intolerance diagnosed in the second or third trimester of pregnancy that does not fulfil the criteria of overt diabetes (Cefalu et al., 2019). Lifestyle interventions focusing on diet and physical activity are usually recommended as the primary therapeutic strategy (Blumer et al., 2013; Gilbert et al., 2019; Cefalu et al., 2019; American Diabetes Association, 2020) for glucose control during pregnancy. When lifestyle interventions fail to achieve glycemic targets (Lehmann et al., 2009; Blumer et al., 2013; Metzger et al., 2007; American Diabetes Association, 2020), glucose-lowering medication is initiated. In accordance with the American Diabetes Association (ADA) guidelines, insulin is prescribed more frequently in Switzerland, as it does not cross the placenta (Cefalu et al., 2019; American Diabetes Association, 2020), although metformin can also be prescribed (Webber et al., 2015). According to a recent study and similarly to our practice, insulin is the most frequently used glucose-lowering medication during GDM pregnancy across countries (Cesta et al., 2019).

Women with GDM are more likely to suffer from mental health symptoms. Indeed, women with GDM have higher rates of depression during pregnancy and in the postpartum period, compared to women

* Corresponding authors.
E-mail addresses: leah.gilbert@chuv.ch (L. Gilbert), argyro.nikolaou@hcuge.ch (A. Nikolaou), dan.quansah@chuv.ch (D.Y. Quansah), jean-benoit.rossel@unisante.ch (J.-B. Rossel), antje.horsch@chuv.ch (A. Horsch), jardena.puder@chuv.ch (J.J. Puder).
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without GDM (Bennett et al., 2004; Damé et al., 2017; Daniells et al., 2003; Wilson et al., 2019; Alexandre et al., 2017). Mental health symptoms therefore represent an important factor to consider in women with GDM, as they may interfere with their capacity to adhere to lifestyle interventions (Molyneaux et al., 2018). Indeed, symptoms of depression may reduce an individual's coping abilities and may lead to disordered eating behaviors and lower dietary quality (Fowles et al., 2011). Depression may also lead individuals to eat as a strategy to relieve themselves of negative symptoms (Christenson et al., 2016) and may decrease women's motivation to conduct physical activity (Carter and Swardfager, 2016). Thus, mental health symptoms may impact both diet and physical activity and lead to higher glycaemia during pregnancy (Blumer et al., 2013; Ruchat and Mottola, 2013). Secondly, mental health symptoms may be directly related to worsened metabolic control in women with GDM. Overall, depression is associated with a higher risk of future GDM (Hinkle et al., 2016). Similarly, higher anxiety and depression scores, as well as stress perception, are associated with higher glycaemia during pregnancy (Horsch et al., 2016; Hinkle et al., 2016). However, even if mental health symptoms can have a direct impact on glycaemia and adherence to lifestyle interventions, it is not clear if it increases the need for glucose-lowering medication in women with GDM. In addition, we are not aware of any study investigating whether the presence of clinically relevant symptoms of depression might augment the need for glucose-lowering medication. This could have an important impact on the identification and care of these women.

Conversely, there might also be an association between the need for glucose-lowering medication and subsequent mental health symptoms. Indeed, our clinical experience shows that many women are willing to adjust their lifestyle in order to avoid medication and particularly the burden of insulin injections. In addition, the need for glucose-lowering medication could lead to a feeling of failure. To our knowledge, only one study showed that insulin use was not a predictor for postpartum depression in women with GDM (Nicklas et al., 2013). Thus, the potential impact of glucose-lowering medication on the mental health of women with GDM and in the postpartum period remains understudied. It is important to study this question, as mental health symptoms have been shown to be higher in the postpartum period in women with GDM (Wilson et al., 2019) and may have important adverse effects on the health of the mother (Christenson et al., 2016; Herring et al., 2008) and the infant (Grace et al., 2003; Cooper and Murray, 1998; Cato et al., 2019). To study these questions, we chose both symptoms of depression (Hinkle et al., 2016; Blumer et al., 2013; Ruchat and Mottola, 2013) and well-being (Robertson et al., 2012; Hochberg et al., 2012) as markers of mental health, as they had either shown their impact on glycemic control or were studied in patients with diabetes.

This study was therefore conducted to 1) investigate if mental health symptoms, described here as high symptoms of depression and low well-being scores, in women with GDM, predict a need for glucose-lowering medication during pregnancy and 2) describe the overall trajectory of mental health in these women and investigate if the need for glucose-lowering medication independently predicts mental health symptoms during and after pregnancy. We also studied if clinically relevant symptoms of depression would influence these associations, i.e., if they are different in the presence of symptoms of depression.

2. Materials and methods

2.1. Setting and patient population

This prospective clinical cohort study included pregnant women diagnosed with GDM according to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) and ADA guidelines (Metzger et al., 2010; Blumer et al., 2013; American Diabetes Association, 2019). These women were taken care of in the Diabetes and Pregnancy Unit at the Lausanne University Hospital (Switzerland) between 2016 and 2019. The Human Research Ethics Committee of the Canton de Vaud, Switzerland approved the study protocol (326/15).

2.2. Inclusion and exclusion criteria

This study is part of an ongoing prospective clinical cohort of women with GDM, for which participating women provided signed consent for data usage. Out of the 959 participating women, we selected those who corresponded to our eligibility criteria (n = 875) (please see Fig. 1), who presented after January 2016 (when we started systematically distributing mental health questionnaires) (n = 800), and were present during predefined time points that are essential (first and last GDM visit) in order to have baseline mental health assessed and valid information regarding glucose-lowering medication (the two main aims of the study). Thus, 341 women with GDM were included in the current analysis.

2.3. GDM management/clinical care

At the first clinical visit after the confirmation of GDM diagnosis, women receive information on GDM from a nurse or medical doctor specialized in GDM and are taught to perform capillary blood glucose (CBG) measures. Women are then asked to monitor their CBG 4 times per day (fasting blood glucose (FBG) in the morning and 2-hour (or 1-hour) postprandial blood glucose after each meal) (Arditi et al., 2017; American Diabetes Association, 2020). A week later, women are seen by a dietician and receive recommendations regarding their CBG, eating habits and weight gain (Blumer et al., 2013) and are encouraged to increase their physical activity (Colberg et al., 2013). If despite lifestyle changes (diet and physical activity) glucose values remain above targets two or more times during a 1–2-week period, glucose-lowering medication is introduced (Lehmann et al., 2009; Metzger et al., 2007). Glucose-lowering medication type depends on glucose values (i.e., insulin in case of relatively high values), patient characteristics (i.e., Body Mass Index (BMI)) and patient preference, but in the vast majority of cases insulin is the preferred treatment over metformin. Short-acting insulin analogues are introduced and adapted to achieve a 2-hour postprandial glucose value $\leq$7 mmol/l (alternatively 1-hour postprandial glucose $\leq$8 mmol/l), and long-acting insulin analogues to achieve FBG $\leq$5.3 mmol/l (Carroll and Kelley, 2014; American Diabetes Association, 2019, 2020). Women are then followed until delivery and an oral glucose tolerance test (oGTT) is performed between 6 and 8 weeks postpartum (American Diabetes Association, 2020).

2.4. Measures

2.4.1. Maternal symptoms of depression

The Edinburgh Postnatal Depression Scale (EPDS): The EPDS was used in the current study to measure symptoms of depression. The questionnaire has been validated in pregnant women (Bunevicius et al., 2009), as well as in a French population, and good psychometric properties have been reported (Guedeney and Fermanian, 1998). Symptoms of depression in the preceding 7 days were assessed (Cox, Holden, and Sagovsky, 1987) at the women's first GDM clinical visit and at the 6–8 weeks postpartum clinical visit. We distributed this self-report questionnaire in French and in English. For women who did not understand these languages, we ensured that a certified professional translator helped them complete it. Each item of this questionnaire is scored on a 4-point scale, the minimum and maximum total scores being 0 and 30, respectively. For our interaction analysis, we additionally created a dichotomous variable using a cut-off of $\geq$ 11 to separate women with and without clinically relevant depression scores (Bunevicius et al., 2009). For this cut-off, the terminology "clinically relevant symptoms of depression" was chosen, given that clinical interviewing represents the gold standard to diagnose depression (Watson et al., 2009).

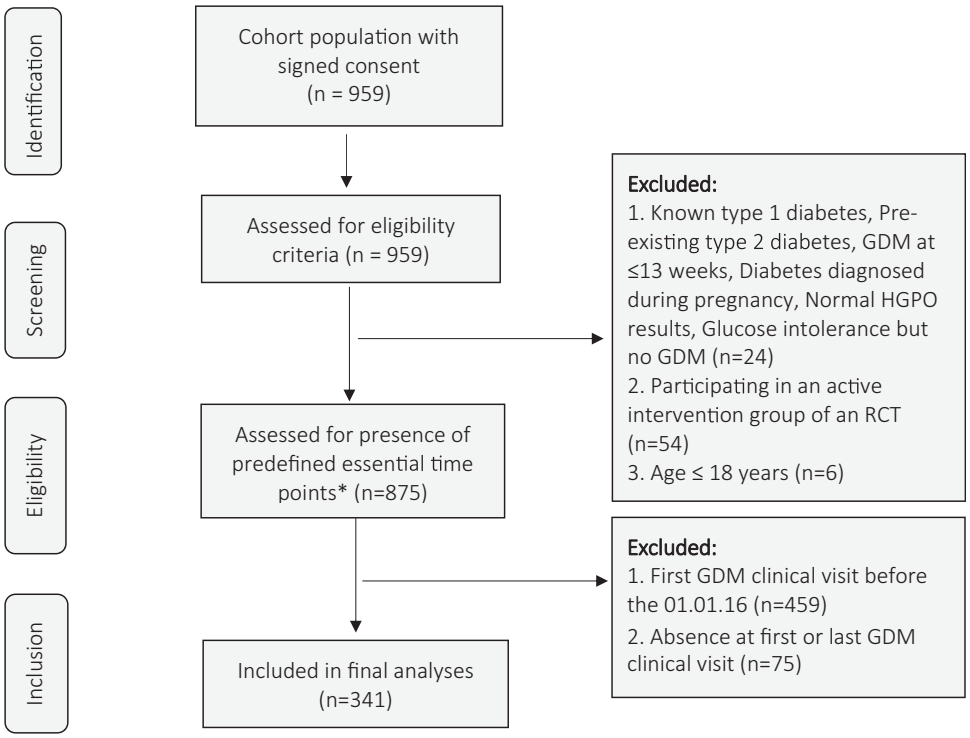

Fig. 1. Flow chart describing how the study participants were selected. * Systematic distribution of mental health questionnaires started on 01.01.2016 and women that were followed before this time point were excluded. First and last GDM clinical visit were the predefined essential time points providing indispensable information regarding the two main aims: baseline mental health and valid information regarding glucose-lowering medication. Women that were absent at either one of these time points were therefore also excluded.

2.4.2. Maternal well-being index

The World Health Organisation Well-Being Index-Five (WHO-5): The WHO-5 was used to measure well-being in our sample, as this questionnaire has shown adequate validity as an outcome measure in clinical studies (Henkel et al., 2003; Topp et al., 2015). It has been used extensively in endocrinology, and the French version has shown good psychometric properties (Topp et al., 2015; Hochberg et al., 2012). This 5-item self-report questionnaire assessed the subjective well-being of the participants (Topp et al., 2015) at the first and last GDM clinical visit and at the 6–8 weeks postpartum clinical visit. In accordance with the ethnical diversity of our patients, we used validated versions of the questionnaire in several languages. The items are measured on a 5-point Likert scale ranging from 0 '*at no time*' to 5 '*all of the time*'. The final score is then calculated by multiplying the total score by 4; thus, the final score ranges from 0 to 100.

2.4.3. Glucose-lowering medication

Information regarding glucose-lowering medication intake was retrieved from the medical records at the last GDM clinical visit. With this information, two types of variables were generated. First, a dichotomous (yes, no) variable named "glucose-lowering medication" was created to know if women did or did not take glucose-lowering medication during their pregnancy. For additional and more detailed analysis, a second variable was comprised of four categories: no glucose-lowering medication intake (1), metformin only (2), long-acting (basal) bedtime insulin (± metformin) (3), and short-acting (meal) insulin (± long-acting bedtime insulin and/or metformin) (4). These categories of glucose-lowering medication were formed based on degrees of burden to the participants: the injections with short-acting insulins were considered being most burdensome (as women have to carry syringes with them wherever they go and inject before the meals, often outside of their home), and no glucose-lowering medication, was considered as putting a lower strain on women and metformin was in between. Indeed, previous research has shown that metformin is better accepted in women with GDM and that insulin is more burdensome (Rowan et al., 2008). This variable is named "detailed glucose-lowering medication" and the reference category was 1 =no glucose-lowering medication intake.

2.4.4. Sociodemographic, medical and anthropometric variables

At the first GDM clinical visit, maternal age, weeks of gestation, educational level, social support, prior GDM diagnosis, and family history of diabetes information were collected during the clinical consultation or extracted from medical records. Furthermore, glycated haemoglobin (HbA1c) was measured using a chemical photometric method (conjugation with boronate; Afinion®) (Clinical Chemistry and Clinical Toxicology Devices Panel, 2016; Wood et al., 2012) and Body Mass Index (BMI) at first GDM clinical visit was calculated based on measured height and weight using the formula weight (kg)/[height (m)]^2.

2.5. Data analysis

All analyses were carried out with SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Descriptive statistics were conducted for socio-demographic variables (Table 1). Continuous and normally distributed variables were described as means and standard deviations and ordinal outcomes were described as frequencies and percentages. Statistical significance was set at $p < 0.05$.

Regarding the first objective, investigating the prospective association between mental health symptoms and the subsequent need for glucose-lowering medication, we conducted logistic regression analyses with the dichotomous glucose-lowering medication variable as the dependent variable. To see if this relationship was different in women with higher depression scores, we added the "clinically relevant symptoms of depression" interaction term (dichotomous variable created from the EPDS scale) for the association between well-being and the glucose-lowering medication dichotomous variable. This was possible, as the correlation between the predictor (well-being scores) and the interaction term (clinically relevant symptoms of depression) was only small to moderate (correlation coefficient $r = -0.47$). This interaction term could not be added when the depression scores were the predictor, as the correlation was too high between this predictor and the

interaction term (clinically relevant symptoms of depression; correlation coefficient $r = 0.81$) and both of these measures; depression scores and clinically relevant symptoms of depression are derived from the same questionnaire. Given that none of the interactions were significant in our first objective, we did not conduct further stratification analyses.

Regarding the second objective, we first evaluated the trajectory of the depression and well-being scores over time during and after pregnancy in women with GDM using a linear mixed effects model. Indeed, it seemed important to first gain knowledge about the general trajectory of mental health in women with GDM in pregnancy and in the postpartum period. Then, we assessed the prospective association between the use of glucose-lowering medication and subsequent mental health at the end of pregnancy (well-being scores) and in the postpartum period (well-being and depression scores). We performed linear regressions with occurrence of glucose-lowering medication as a binary predictor (yes, no), and also with the detailed glucose-lowering medication as a categorical predictor. Finally, to see if the impact of glucose-lowering medication (yes, no) on mental health was different if clinically relevant symptoms of depression were present, we added the "clinically relevant symptoms of depression" interaction term. If any of the interactions were significant, we conducted further stratification analyses, separating women with clinically relevant symptoms of depression from those without. This was only the case for the association between the dichotomous glucose-lowering medication variable during pregnancy and well-being at the postpartum clinical visit.

For all regressions, we used two models (model 1 & 2). In model 1, we adjusted for maternal age and gestational weeks at the first GDM clinical visit (Crowther et al., 2005; Ruohomäki et al., 2018). In model 2, we added variables that were significantly correlated with the respective dependent variable. We tested the following potential confounder variables: family history of diabetes, prior GDM diagnosis, BMI and HbA1c at the first GDM clinical visit, social support, and educational level. For the first objective, family history of diabetes, social support, educational level, and HbA1c were added as confounders in model 2. For the second objective, only family history of diabetes was added as a confounder in model 2 when the dependent variable was well-being. There was no model 2 when the dependent variable was depression, as none of the additional confounders were correlated with this score. In an additional step, we also adjusted for baseline mental health variables at the first GDM clinical visit in order to investigate if the associations changed. Given that this did not change the results (data not shown), we used the simpler model (model 2). In analogy, we also tested completely unadjusted models. However, as is common practice, we adjusted for age and gestational age in our basic model 1.

3. Results

Table 1 shows detailed descriptive information regarding sociodemographic and medical parameters. Women had a mean age of 33.62 ± 5.34 years and a mean gestational age of 28.85 ± 3.38 weeks at the first GDM clinical visit and a mean gestational age of 36.44 ± 1.28 at the last GDM clinical visit. 25.2% of women suffered from clinically relevant symptoms of depression and 47.8% of women took glucose-lowering medication during their GDM pregnancy. In our sample, 120 (35.2%) women were pregnant for the first time and 167 (49%) had no previous babies. Out of 174 (51%) women who were multiparas, 9.2% ($n = 16$) had previous GDM.

3.1. Prospective associations between mental health and the subsequent need for glucose-lowering medication during pregnancy

Women's mental health at the first GDM clinical visit did not predict a subsequent need for glucose lowering medication during pregnancy, neither for the depression (OR=1.0 (CI=0.96 – 1.04; $p = 0.94$) nor for the well-being scores (OR=0.99 (CI=0.98–1.01; $p = 0.29$). These results remained similar in model 2 (OR=0.99 (CI=0.93 – 1.04; $p = 0.62$) and (OR=0.99 (CI=0.98 – 1.01; $p = 0.30$)).

The association between the well-being score and the subsequent need for glucose-lowering medication was not significantly different between women with or without clinically relevant symptoms of depression at the first GDM clinical visit (p for interaction = 0.80).

3.2. Prospective associations between the need for glucose-lowering medication and subsequent mental health during and after pregnancy

Mental health improved significantly over time in the whole sample (see Fig. 2a & 2b). Thus, the depression scores decreased by 26% between the first GDM clinical visit and the postpartum clinical visit (B=−1.74, CI= −2.22 to −1.26, $p < 0.01$). Specifically, mean scores changed from a 7.43 ± 5.46 at the first GDM clinical visit to 5.90 ± 4.40 at the postpartum clinical visit. The well-being scores increased overall by 7% between the first GDM clinical visit and the postpartum clinical visit (B=2.49, CI= 1.34 – 3.64, $p < 0.01$). More specifically, the mean

Table 1
Descriptive maternal sociodemographic and medical parameters.

	All	With glucose-lowering medication	Without glucose-lowering medication
	Mean (SD) or n (%)	*Mean (SD) or n (%)*	*Mean (SD) or n (%)*
Maternal sociodemographic and medical parameters			
Age (years)	33.62 (5.34)	33.39 (5.27)	33.84 (5.41)
Educational level			
No education	3 (0.9%)	1 (0.6%)	2 (1.1%)
Compulsory education not completed	17 (5%)	8 (4.9%)	9 (5.1%)
Compulsory education completed	60 (17.6%)	33 (20.3%)	27 (15.2%)
Secondary school	38 (11.1%)	18 (11%)	20 (11.2%)
Apprenticeship	55 (16.1%)	29 (17.8%)	26 (14.6%)
University degree	113 (33.1%)	46 (28.2%)	67 (37.6%)
Social support			
Lives: alone without support, alone with support, with partner	13 (3.8%), 14 (4.1%), 292 (85.6%)	9 (5.5%), 2 (1.2%), 138 (84.7%)	4 (2.2%), 12 (6.7%), 154 (86.5)*
Obstetric variables			
Gestational age at first GDM clinical visit	28.85 (3.38)	28.13 (3.85)	29.51 (2.74)*
Gestational age at last GDM clinical visit	36.44 (1.28)	36.34 (1.31)	36.53 (1.25)
GDM variables			
HbA1c at first GDM clinical visit % - (mmol/mol)	5.4 (0.43) – (35 (4.32))	5.5 (0.51) – (37 (5.09))	5.3 (0.31) (34 (3.11))*
Family history of diabetes: None, First and Second degree relative	126 (37%), 122 (35.8%), 71 (20.8%)	56 (34.4%), 63 (38.7%), 33 (20.2%)	70 (39.2%), 59 (33.1%), 38 (21.3%)
Mental health variables			
Depression score at first GDM clinical visit	7.43 (5.46)	7.49 (5.75)	7.38 (5.20)
Women with clinically relevant symptoms of depression (cut-off of ≥ 11) at the first GDM clinical visit	77 (25.2%)	42 (28.8%)	35 (22%)
Detailed glucose-lowering medication for the overall sample		*n (%)*	
No glucose-lowering medication intake (1)		178 (52.2%)	
Metformin only (2)		15 (4.4%)	
Long-acting (basal) bedtime insulin (±metformin) (3)		64 (18.8%)	
Short-acting (meal) insulin (±long-acting bedtime insulin and/or metformin) (4)		84 (24.6%)	

Continuous and normally distributed variables were described as means and standard deviations and ordinal outcomes were described as frequencies and percentages. *Indicates a significant difference ($p < 0.05$) between the subgroups with and without glucose-lowering medication, respectively.
BMI: body mass index.

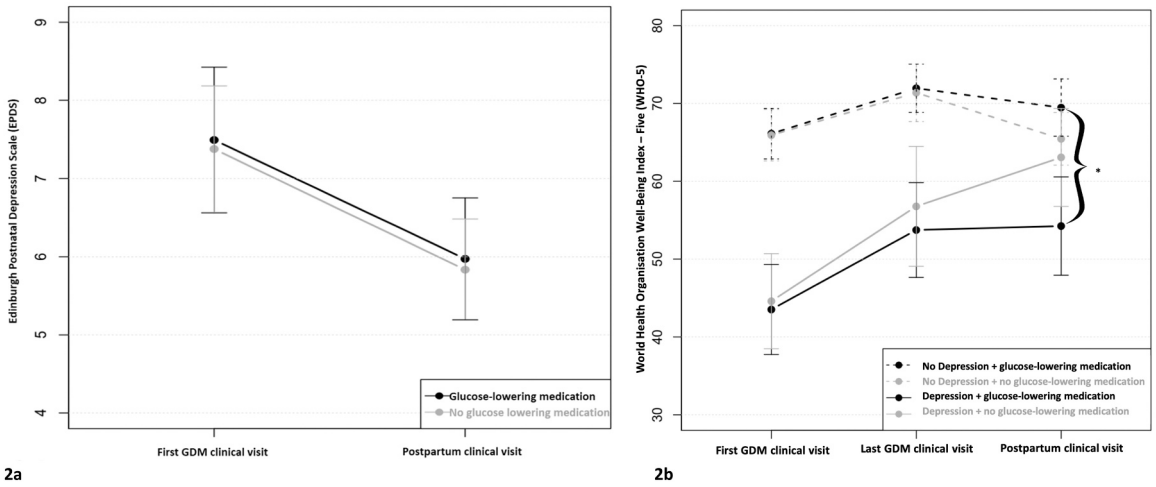

Fig. 2. Overall effect of time showing significant decreases in mean depression (Fig. 2a; Edinburgh Postnatal Depression Scale (EPDS)) and well-being (Fig. 2b; World Health Organization Well-being Index-Five; (WHO-5)) scores in the overall sample (B=−1.74, CI= −2.22 to –1.26, p < 0.01 and B=2.49, CI= 1.34 – 3.64, p < 0.01). For illustrative purposes, women with and without glucose-lowering medication are separated. Of all interaction effects tested, the only significant finding relates to the presence or not of clinically relevant symptoms of depression (named "depression" in the figures) at the first GDM visit on the association between glucose-lowering medication in pregnancy and well-being at the postpartum visit (p for interaction = 0.01 and shown as a star on Fig. 2b). Values are shown as means and standard errors.

well-being scores changed from 60.55 ± 20.368 at the first GDM clinical visit to 67.59 ± 17.96 at the last GDM clinical visit, and to 65.43 ± 18.79 at the postpartum clinical visit.

The need for glucose-lowering medication during pregnancy had no impact on subsequent mental health during and after pregnancy. This was the case for the depression scores at the postpartum clinical visit (B=0.29 (CI=−0.76 to 1.34; $p = 0.59$)), the well-being scores at the end of pregnancy (B=2.01 (CI=−6.72 to 2.69; $p = 0.40$) in model 1, B= 2.26 (CI=−6.84 to 2.32; $p = 0.33$) in model 2) and the well-being scores at the postpartum clinical visit (B=−0.15 (CI=−4.59 to 4.30; $p = 0.95$) in model 1, B= 0.25 (CI=−4.18 to 4.69; $p = 0.91$) in model 2). These results remained unchanged when controlled for baseline mental health at the first GDM clinical visit (data not shown).

When looking at the detailed glucose-lowering medication, we found very similar results (see Table 2), with the exception of metformin, used in 13 women, that was associated with improved well-being in the postpartum period compared to no glucose-lowering medication ($p = 0.03$, see Table 2).

Regarding the interaction effect of clinically relevant symptoms of depression on the association between glucose-lowering medication and mental health, we found no interaction effect on the depression score at the postpartum clinical visit ($p = 0.93$), nor on the well-being score at the end of pregnancy ($p = 0.49$). However, in women with clinically relevant symptoms of depression, glucose-lowering medication in pregnancy was associated with a lower improvement in the well-being score at the postpartum clinical visit compared to women without clinically relevant symptoms of depression (p for interaction = 0.01, Fig. 2b). Further stratification analysis revealed that, in women with clinically relevant symptoms of depression, glucose-lowering medication led to a non-significant decrease in well-being of −8.82 points ($p = 0.063$), whereas in women without symptoms of depression, glucose-lowering medication lead to a non-significant increase in the well-being scores of 4.02 points ($p = 0.12$).

Table 2
Prospective associations between detailed glucose-lowering medication during pregnancy and subsequent mental health.

	Model 1	Model 2
	Well-being scores at the last GDM clinical visit	
Metformin vs none	B = −0.62 (CI = −11.66 to 10.43)	B = −0.99 (CI = −11.63 to 9.65)
Long-acting Insulin vs none	B = −2.95 (CI = −8.86 to 2.96)	B = −1.99 (CI= −7.79 to 3.82)
Short-acting Insulin vs none	B = −0.54 (CI = −6.22 to 5.13)	B = −0.24 (CI= −5.84 to 5.36)
	Well-being scores at the postpartum clinical visit	
Metformin vs none	B = 11.65 (CI = 1.06 – 22.24)*	B = 11.42 (CI = 0.92 – 21.92)*
Long-acting Insulin vs none	B = −1.97 (CI = −7.60 to 3.67)	B = −1.41 (CI = −7.16 to 4.34)
Short-acting Insulin vs none	B = 1.26 (CI = −4.04 to 6.55)	B = 1.57 (CI = −3.81 to 6.95)
	Depression scores at the postpartum clinical visit	
Metformin vs none	B = −0.15 (CI = −2.64 to 2.34)	–
Long-acting Insulin vs none	B = 1.00 (CI = −0.34 to 2.31)	–
Short-acting Insulin vs none	B = 0.46 (CI = −1.72 to 0.80)	–

Results reported as β-Coefficient (95% confidence interval) from a general linear model.
The following three categories are compared to "no glucose-lowering medication" (termed "none") being used as a reference category (1), metformin only (2), long-acting (basal) bedtime insulin (± metformin) (3), and short-acting (meal) insulin (± long-acting bedtime insulin and/or metformin) (4).
Model 1 adjusted for maternal age and gestational age at the first GDM clinical visit.
Model 2 adjusted for maternal age, gestational age, family history of diabetes and well-being at the first GDM clinical visit, except for the analyses with the depression score at the postpartum clinical visit for which no additional confounders were added, as no additional confounders were significantly correlated to this dependent variable.
* p < 0.05

4. Discussion

This study investigated a clinical cohort of women with GDM and demonstrated that mental health symptoms at the first GDM clinical visit did not predict a later need for glucose-lowering medication. Furthermore, mental health improved throughout pregnancy and in the early postpartum period. Importantly, the need for glucose-lowering medication was not associated with future mental health symptoms during and after pregnancy. Clinically relevant symptoms of depression at the first GDM clinical visit did not interact with these investigated associations, except for the well-being scores at the postpartum clinical

visit, which improved less in women with clinically relevant symptoms of depression.

To the best of our knowledge, this is the first study to report that there is no association between mental health symptoms and the subsequent need for glucose-lowering medication in women with GDM. Previous research shows that mental health symptoms are associated with both a lower adherence to lifestyle interventions and thus can lead to higher glycaemia (Molyneaux et al., 2018; Carter and Swardfager, 2016; Ruchat and Mottola, 2013), and, that mental health symptoms are also directly associated with a higher glycaemia in pregnancy (Hinkle et al., 2016; Horsch et al., 2016). Both, low adherence to lifestyle interventions and higher glycaemia would be expected to lead to a more frequent need for glucose-lowering medication. Surprisingly, this was not the case in our population, nor was this influenced by the presence of clinically relevant symptoms of depression. These symptoms were present in 25.2% of our cohort and the mean score was 7.43 at the first GDM clinical visit, which is comparable to other studies in women with GDM and, for some, in normal pregnancies (Damé et al., 2017; Varela et al., 2017; Mak et al., 2019; Wilson et al., 2019). In our sample, the symptoms of depression declined by 26% to a mean score of 5.9 at the postpartum clinical visit. This score is similar to a previous sample of GDM women in the postpartum period (Nicklas et al., 2013). In the current sample, the well-being scores also augmented by 7% between the first GDM clinical visit and the postpartum clinical visit, and attained similar scores as previously reported in healthy pregnancies and in the postpartum period (Mortazavi et al., 2015). The scores at the last GDM clinical visit cannot be compared to previous research as we are not aware of such studies. The fact that well-being at the first GDM clinical visit and the postpartum clinical visit in our sample is not lower than that of normal pregnancies is reassuring, given that women with GDM usually have higher depression scores than the general population (Bennett et al., 2004; Damé et al., 2017), and that depression is known to be negatively associated with well-being in pregnancy (Wersebe et al., 2018). We believe that the improvements found in mental health over time could be due to the social support the patients receive from clinicians (Barger et al., 2014). Indeed, women are seen a for a few clinical appointments during their pregnancy and receive tailored advice and attention from our team of specialized clinicians. This could also have improved well-being and lowered depression in our population, despite the need for frequent glucose monitoring and lifestyle adjustments.

The improvements found in mental health were not influenced by glucose-lowering medication intake, as glucose-lowering medication did not predict the future well-being or depression scores during or after pregnancy. This result is comparable to one previous study in women with GDM showing that use of insulin during pregnancy was not associated with symptoms of depression in the postpartum period (Nicklas et al., 2013), while overall well-being or mental health during pregnancy has not been previously investigated. These findings may reassure clinicians when they need to initiate glucose-lowering medication with patients, as mental health does not seem to be affected by medication intake, at least in our population. This could possibly mean that women do not view glucose-lowering medication as a failure of their lifestyle behavior change, but rather as another acceptable solution to lower their glucose. Also, glucose-lowering medication may bring them some relief if lifestyle adaptations alone did not yield the desired effect (Rowan et al., 2008). Another novel, yet, secondary finding was that the use of metformin was associated with improved well-being in the postpartum period. Although, this result is in line with previous research showing that metformin is the preferred type of medication in women with GDM (Rowan et al., 2008), this result should be interpreted with caution and needs to be replicated in future research, as this concerned only a very small number of women (n = 13, 3.8%).

The presence of clinically relevant symptoms of depression did not interact with our findings except with the association between glucose-lowering medication during pregnancy and the well-being scores in the postpartum period. Indeed, the results demonstrated that in women with both clinically relevant symptoms of depression and glucose-lowering medication, there was a lower improvement in the postpartum well-being scores compared to women with no clinically relevant symptoms of depression. In these women, the combination of glucose-lowering medication, higher depression scores and having to care for a newborn might cumulate and contribute to the lower increase and lower absolute well-being scores. Hajos et al. showed that a score of 50 on the WHO-5, which is close to the mean score of 54 in our subgroup of women, can be interpreted as suboptimal well-being and warrants further testing for depression (Hajos et al., 2013). This is especially important, as depression in the postpartum period can have adverse impacts on the mother's cardio-metabolic health (Christenson et al., 2016; Herring et al., 2008; Carter and Swardfager, 2016). Depression in the postpartum may also lead to negative consequences for the infant, such as lower duration of breastfeeding (Cato et al., 2019) and to relationship difficulties between the mother and her infant, which have shown to be prospectively associated with a suboptimal development of cognitive (for example language development) and emotional functioning of the infant (Grace et al., 2003; Cooper and Murray, 1998). Thus, these women should be identified and may need psychological interventions.

4.1. Strengths and limitations

This study has several strengths. First, we included a "real-life", multiethnic and diverse population in which patients completed the questionnaires either in their native language or with the help of a certified professional translator. Second, we included influential confounding variables; in our basic model we controlled for variables of interest in the GDM population (Crowther et al., 2005; Ruohomäki et al., 2018), and in our second model, we added confounding variables that correlated significantly to our dependent variables. Finally, we also made sure that the well-being and depression scores at the first GDM clinical visit did not alter the results by controlling for these results with a third model (data not shown).

Limitations of the study include the lack of information about the women's physical activity and diet behaviors, which could have been important confounders for the intake of glucose-lowering medication. Furthermore, we do not have information about mental health variables before the first GDM clinical visit or mental health measurements other than depression or well-being scores after their GDM diagnosis (such as anxiety symptoms), which could be seen as a limitation. The data about metformin needs to be interpreted with caution, as this only concerns 13 (3.8%) of women and the choice to treat with metformin might be biased. As no exclusion criteria were applied for the timings of the clinical visits, this could have had an influence on the women's mental health variables. Women came for their first GDM clinical visit at a mean of 28.85 (3.38) weeks of gestation. Allover, 8 (2.4%) women came before 20 or 24 weeks of gestation, as no women came between 20 and 24 weeks of gestation and 29 (8.7%) came later than 32 weeks of gestation for their first GDM clinical visit. The last GDM clinical visit took place at a mean of 36.44 (1.28) weeks; all of the women came between 32 and 40 weeks of gestation and of those, 55 (23.7%) came before 36 weeks of gestation. We therefore performed the main analyses in a limited sample of 157 women who came between 24 and 32 weeks of gestation at the first GDM clinical visit and who were at 36 weeks of gestation or more at the last GDM clinical visit and the results did not significantly change.

5. Conclusion

This prospective clinical cohort study found that mental health symptoms did not lead to a higher subsequent need for glucose-lowering medication in women with GDM. This finding is reassuring, as it means that even if mental health symptoms can impact both on lifestyle behavior and on glycaemia, it does not necessarily implicate a higher

need for glucose-lowering medication. Secondly, glucose-lowering medication did not worsen the trajectory of mental health symptoms in this GDM population. This is reassuring for clinicians, as it demonstrates that glucose-lowering medication can be prescribed without the risk of worsening mental health symptoms (symptoms of depression and lower well-being in particular). Even if mental health symptoms did not affect the need for glucose-lowering medication in our pregnant population, it may influence lifestyle behavior and/or glucose values in the postpartum period and thus increase the risk of later prediabetes or diabetes. Similarly, further research should investigate, if the diagnosis of prediabetes and/or diabetes would worsen mental health symptoms in the following months and years and define the trajectory for such a change in order to intervene early. Further studies should also aim at investigating the relationship between use of medication and other mental health symptoms, such as anxiety in the GDM population.

CRediT authorship contribution statement

LG lead the conception and design of the current aims of the study, lead the choices on methodology and supported the data curation, performed the formal analysis, lead the interpretation of data, and wrote the original draft the manuscript. AN delivered the information and literature regarding medication use. DQ lead the data curation, completed the database and equally edited and reviewed the manuscript. JBR supported the interpretation of the data, and edited and reviewed the manuscript. JP is responsible for the overall cohort and participated in the conception and design of the study, choices on methodology, and lead the editing and reviewing of the manuscript and lead the acquiring of funds for the study, lead the supervision of the study. AH equally participated in the conception and design of the study, supported the choices on methodology, also lead the editing and reviewing of the manuscript, and equally supervised the study. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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