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Journal: British journal of health psychology

Year: 2016 Sep

Issue: 21

Volume: 3

Pages: 712-29

DOI: 10.1111/bjhp.12197

Stress exposure and psychological stress responses are related to glucose concentrations during pregnancy

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Acknowledgements

We acknowledge the support of the Department of Obstetrics and Gynaecology of the University Hospital Lausanne and thank all participants. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Abstract

Objectives

The role of stress in the development of gestational diabetes mellitus (GDM) has so far been neglected. We investigated the impact of stress exposure (pregnancy-related and -unrelated major life events), psychological stress responses (perceived stress, subjective experience of stress, anxiety, depression, sleep), and physiological stress responses (salivary cortisol, plasma copeptin levels) on glucose concentrations during pregnancy.

Design

Cross-sectional study, including 203 pregnant women at the maternity department of a Swiss University Hospital.

Methods

All women underwent routine screening for GDM with a 75-g oral glucose tolerance test at 24 to 30 weeks gestation. Pregnancy-related and -unrelated major life events, perceived stress, general psychological distress, anxiety, depression, and amount of sleep were assessed by validated self-report questionnaires. Cortisol was measured using fasting and bedtime saliva samples, and copeptin using fasting plasma. All data were collected before communication of the screening test results.

Results

Significant positive associations were found between the number of pregnancy-related major life events with fasting glucose, while there was no association with pregnancy-unrelated major life

events. More anxiety and depressive symptoms, a higher general level of distress and a shorter duration of sleep were related to fasting glucose, although the latter two were no longer significant when age and BMI were controlled for. However, physiological stress responses were not associated with glucose concentrations. When testing for unique associations with fasting glucose, more general distress and shorter duration of sleep independently accounted for higher fasting glucose levels. Finally, when comparing women with and without GDM, we found that women who subsequently received the diagnosis of GDM reported more pregnancy-related life events.

Conclusions

Some indicators of stress exposure and psychological stress responses were associated with fasting glucose concentrations in pregnant women, thus representing important risk factors for GDM development.

Statement of contribution

What is already known on this subject?

- Only approximately half of women with gestational diabetes mellitus (GDM) report any known risk factors
- Women after GDM diagnosis reported more major life events compared to healthy pregnant controls.

What does this study add?

- Stress exposure and psychological stress responses were associated with fasting glucose concentrations in pregnant women
- These represent important risk factors for GDM development and potential targets for intervention

Introduction

Gestational diabetes mellitus (GDM), which affects approximately 3-7 % of pregnancies, is related to an increased risk of adverse pregnancy outcomes (Catalano et al., 2012) and linked to a seven-fold increased risk of developing type 2 diabetes mellitus (Bellamy, Casas, Hingorani, & Williams, 2009). The development of GDM is associated with genetic (family history of diabetes), demographic and sociocultural factors (increased age, migrant status, low socioeconomic status), certain lifestyle behaviours (lack of physical activity, high fat intake), and anthropometric parameters (excess weight, gestational weight gain, and low maternal birth weight) (American Diabetes Association, 2015; Jenum et al., 2012; Ladson et al., 2014; Most & Langer, 2012; Tobias, Zhang, van Dam, Bowers, & Hu, 2011). However, only approximately half of women with GDM report any of the known risk factors (Dode & dos Santos, 2009). Previous studies have pointed to stress as a potential, but rarely explored this as a risk factor for metabolic disturbances and more research into stress exposure and psychological stress response as GDM risk factors is needed (Akiko S. Hosler, Seema G. Nayak, & Anne M. Radigan, 2011; Spirito et al., 1991).

Any physical or psychosocial stimulus can be stressful, provided that it is perceived as threatening for the homeostasis and the survival of the organism (Lazarus, 1993). The allostatic load model (B. S. McEwen, 2012) proposes an interaction between (a) exposure to environmental stressors (e.g. major life events), (b) psychological stress responses (e.g. perceived stress, general psychological distress or negative mood such as anxiety and depression), (c) disadvantageous behavioural stress responses (e.g. lifestyle behaviour), and (d) physiological stress responses of the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol is the most frequently used biomarker of the physiological stress responses of the HPA axis. Another

such biomarker is copeptin, which is a surrogate marker for arginin vasopressin production. Cortisol and arginin vasopressin or copeptin, respectively have been implicated in the potential link between physiological stress responses and increased glucose levels. Cortisol and arginin vasopressin can antagonise insulin action, augment insulin resistance, and even suppress insulin secretion in pancreatic beta cells, thereby leading to elevated blood glucose levels (Enhorning et al., 2011; Bruce S. McEwen, 2015). Furthermore, copeptin levels predict increased risk for diabetes mellitus independently of established risk factors (Enhörning et al., 2010). However, associations between these physiological stress responses and increased glucose concentrations have so far not been investigated in pregnant women.

Physiological stress responses have the adaptive function of mobilizing resources towards tackling the stressor. However, prolonged stress-related psychophysiological alterations may lead to allostatic load, the wear and tear cost of adaptation resulting from chronic overactivity, or inactivity of physiological stress systems. In the longer term, allostatic load poses an increased risk for functional or mental disorders or metabolic diseases such as GDM (B. S. McEwen, 2012). This hypothesised pathway, which may lead to the development of GDM, includes stress exposure, psychological stress responses, adapted lifestyle behaviour as well as physiological stress responses.

In the non-pregnant population, exposure to acute psychological stress is associated with increased glucose levels and higher risk of diabetes mellitus (Faulenbach et al., 2012). During pregnancy, two studies found that women with known GDM reported more major life events compared to healthy pregnant controls (A. S. Hosler, S. G. Nayak, & A. M. Radigan, 2011; Spirito et al., 1991). This may be mediated by the responses of the HPA axis, as associations between life events (stress exposure) and/or negative mood (anxiety, depression) and salivary

cortisol levels during healthy pregnancy have been demonstrated (Giesbrecht, Campbell, Letourneau, Kooistra, & Kaplan, 2012; Obel et al., 2005; Pluess et al., 2012). Importantly, both GDM studies used a retrospective design, and one can assume that the knowledge of a GDM diagnosis influences the woman's illness perception and creates a recall bias for major life events. Furthermore, antenatal depression is twice as likely to develop in women with known GDM when compared to women without GDM (Kozhimannil, Pereira, & Harlow, 2009). Psychosocial stress (exposure and perception) might therefore be considered as an important, potentially modifiable risk factor contributing to the development of GDM. This study aimed to investigate the impact of stress exposure (major life events, pregnancy-related, and pregnancy-unrelated major life events), psychological stress responses (perceived stress, general psychological distress, negative mood such as anxiety and depression, and amount of sleep), and physiological stress responses (salivary cortisol, plasma copeptin concentrations) on glucose tolerance in women from 24-30 weeks of gestational age before their diagnosis was communicated to them. We hypothesized that higher stress exposure, higher psychological stress responses and higher physiological stress responses would correlate with and predict higher fasting and post-load glucose concentrations during a standardized glucose load. Furthermore, we evaluated whether these relationships persist after statistical adjustment for established risk factors for GDM (demographic, genetic, sociocultural, lifestyle, and anthropometric factors). Finally, we hypothesised that these outcome measures are more prevalent or higher in women that will be diagnosed with GDM compared to those that will not.

Method

Participant consent and recruitment

The results presented here are part of a larger study that took place in the Department of Obstetrics and Gynaecology of a Swiss University Hospital between November 2012 and July 2013 (Horsch et al., 2016). All pregnant women undergoing routine screening for gestational diabetes with a 75-g oral glucose tolerance test at 24 to 30 weeks of gestation were asked to participate in the study whilst waiting for their appointment in the waiting room (between 7.30am and 9.30am). An information sheet and a consent form were given, and women had the opportunity to ask questions about the study. After signing the consent form, a first sample of fasting morning saliva for cortisol analysis was collected. A blood sample was taken for routine analysis of fasting 1- and 2-hour glucose levels and for measurement of fasting plasma copeptin. Participants were then asked to complete the self-report questionnaires, were weighed in light clothes and without shoes, and their height was measured. Afterwards, they were given an additional sampling device and instructed to take another sample of their saliva at around 10 p.m. before going to bed, at least one hour after their last meal and before brushing their teeth. Participants were asked to store the sample in their refrigerator overnight and to return it by post the following morning using a pre-stamped envelope. Results of the glucose tolerance test were given after obtaining the evening cortisol sample only, as obtaining the diagnosis might increase anxiety and stress levels in the short-term (Daniells et al., 2003).

Ethical approval for this cross-sectional study was obtained from the Cantonal Ethics Committee of Vaud, Switzerland (study number 295/12). Women were excluded if they were not able to complete the self-report questionnaires due to French language difficulties or if they had medical problems (such as chronic infections, autoimmune disease, asthma, renal insufficiency) and/or used medications (such as prednisone) that could both influence either their cortisol and/or glucose levels.

Measures

Stress exposure

Major life events. Women were given a list of three negative pregnancy-related major events (suspected growth retardation, vaginal bleeding, premature contractions) as well as ten negative pregnancy-unrelated major life events (death of someone they were close to, serious illness, exposure to abuse, exposure to violence, serious accident, unemployment, disability, alcohol/drug abuse, divorce, moving house) and were asked whether they had been exposed to any of these events in the last 12 months (Koch, Sepa, & Ludvigsson, 2008; Obel et al., 2005).

Psychological stress responses

Perceived Stress Scale (PSS (Cohen, Kamarck, & Mermelstein, 1983)*).* This 14-item self-report questionnaire assesses the level of stress perception in the last month and measures the degree to which an individual perceives and appraises life events as stressful (referred to as the "subjective experience of stress"). Participants were asked to rate how often they have thought or felt in a certain way on a 5-point Likert scale (1 = never; 5 = very often), e.g. "In the last month, how often have you felt nervous and stressed?" A total PSS score is obtained by reversing seven positive items and then summing across all 14 items. Correlations with other measures of objective or stress perception are positive, and adequate internal and re-test reliability has been reported (Cohen et al., 1983). In the present study, Cronbach's α of the PSS was $\alpha = .77$.

Depression, Anxiety and Stress Scale-21 (DASS-21) (Lovibond & Lovibond, 1995). The DASS-21 is a 21-item self report questionnaire designed to measure the severity of a range of

symptoms common to depression, anxiety and negative affectivity (i.e., Stress). Participants were asked to rate the extent to which they experienced symptoms in the last week on a 4-point Likert scale (0 = did not apply to me at all; 3 = applied to me very much or most of the time). Scores for the subscales depression, anxiety and stress were obtained by summing up the relevant items multiplied by two. A total score (indicating general psychological distress) was calculated by summing up the sub-scores (Osman et al., 2012). Adequate psychometric properties have been demonstrated (Henry & Crawford, 2005). In the present study, Cronbach's α of the subscales depression, anxiety and stress, and the total score were .87, .71, .80, and .91 respectively.

Sleep. Three questions from the Pittsburgh Sleep Quality Index (Buysse, Reynolds Iii, Monk, Berman, & Kupfer, 1989) were taken to assess the duration of sleep on week days and on the weekend (total sleep amount was calculated by summing up the hours of sleep on week days and on the weekend), and overall sleep quality (Likert scale from 1= very good to 4 = very bad).

Physiological stress responses

Salivary cortisol levels. Salivary cortisol was measured using Salivette (Sarstedt) collection devices using the passive drool method at two different time points: a fasting sample between 7.30 a.m. and 9.30 a.m. at the hospital just before the 75-g oral glucose-tolerance test at least 90 minutes after awakening, and a bedtime sample at around 10 p.m. After collection, cortisol samples were stored at -20ºC until badge analysis. Analyses took place using a commercial chemiluminescence immunoassay (CLIA; IBL Hamburg, Germany). Inter- and intra-assay coefficients of variation were below 5%.

Plasma levels of Copeptin. Copeptin was measured in a fasting plasma sample by chemiluminescence sandwich immunoassay (Fenske et al., 2009) (BRAHMS AG, Henningsdorf,

Germany) with a lower detection limit of the assay of 0.4 pmol/L and a functional assay sensitivity of <1 pmol/L, as reported by the manufacturer. Assay characteristics included a than 5% intra-assay (<10% interassay) coefficient of variations for concentrations greater than 2.0 (>2.5) pmol/L.

GDM diagnosis

GDM was assessed using a 75-g oral glucose-tolerance test at 24-30 weeks of gestation and diagnosed if one of the following criteria applied: fasting glucose ≥ 5.1 mmol, l-h glucose ≥ 10.0 mmol/l, or 2-h glucose ≥ 8.5 mmol/l using the guidelines of the International Association of the Diabetes and Pregnancy Study Group, the American Diabetes Association and the Endocrine Society (American Diabetes Association, 2015; Blumer et al., 2013; Coustan, Lowe, Metzger, & Dyer, 2010).

Physical activity, sociocultural variables and medical history

Physical activity. Participants were asked how many minutes per week they engaged in moderate physical activity in the last 7 days. This corresponds to the moderate activity subscale of the short form of the International Physical Activity Questionnaire (IPAQ) (Hagströmer, Oja, & Sjöström, 2006).

Sociocultural factors, medical history and anthropometric parameters. Migrant status was assigned if at least one parent was born outside of Switzerland (Bürgi et al., 2012). Education, history of GDM, family history of diabetes (whether a first degree relative had diabetes), and medical diseases and current medication were also assessed. Additional self-

reported data, such as age, pre-pregnancy and current weight, and current height were collected (see Table 1).

Data analysis

All analyses were performed using SPSS Version 22.0 (SPSS, Inc., Chicago, IL, USA).

Statistical analysis

Evening salivary cortisol and copeptin were $\log_{10}$-transformed to improve their distributional properties, and these concentrations were used for all further analyses. Preliminary analyses tested for group differences (GDM vs. non GDM) in baseline demographic and anthropometric characteristics using *t*-tests and χ^2-tests. Next, Pearson correlations, point biserial correlations, and coefficient Phi were used to analyse zero-order associations between glucose concentrations (fasting, 1-h, 2-h), stress exposure, psychological stress responses (stress perception, general psychological distress, sleep quantity), physiological stress responses (cortisol and copeptin concentrations), and confounding variables. Confounding variables included genetic (family history of diabetes), anthropometric (current BMI), demographic and sociocultural (age, educational level, migrant status), and lifestyle characteristics (physical activity). To test for unique associations with glucose concentrations, a two-step hierarchical regression analysis was performed. Stress exposure variables, psychological stress response variables, and physiological stress response variables jointly entered the model in the first step to test for unique associations of each stress-related variable with glucose concentrations. To reduce multicollinearity, the DASS-21 total score replaced the three individual DASS-21 subscales. Confounding variables which were significantly correlated with glucose concentrations entered

the model in the second step. The test of a partial effect of a variable in the 2nd step was mathematically equivalent to the test of ΔR^2 for this variable when all other variables were entered first. Thus, the second step tested whether each stress variable was specifically related with fasting glucose over and above the remaining stress variables and confounding variables.

Missing data

Noncompliance with the study procedure resulted in missing data (for details see results section). Normal-model multiple imputation (*MI*) was used to handle missing data. MI yields unbiased parameter estimates when the operating missing data mechanism is missing completely at random (MCAR; (Enders, 2010; Graham, 2012). Little's test of MCAR (Little, 1988) suggested no violation of this assumption, $\chi^2(695) = 679.39$, $p = .66$. MI was implemented in three steps (see (Graham, 2012) for details): First, the imputation model was made up of variables belonging to the analysis model and auxiliary variables. Second, MI was carried out with NORM 2.0 (Schafer, 1999) in the sequence of summary, expectation-maximization (*EM*) algorithm and data augmentation (*DA*) with imputation. EM converged normally in 19 iterations. Parameters that did not require standard errors (i.e., adjusted multiple R^2, ΔR^2) as well as *M, SD,* and Hedges' *g* for group comparisons were calculated with a single data set imputed directly from EM parameters (with errors). Generating $m = 50$ imputed data sets was regarded as adequate (Graham, 2012). In data augmentation diagnostics, all diagnostic plots for means, variances, and covariances were checked and appeared in order suggesting that the number of DA steps was sufficient and the imputation solution was acceptable. Third, the imputed data sets were analysed using complete-cases procedures and pooling $m = 50$ parameter estimates and

standard errors using SPSS Version 22 (SPSS, Inc., Chicago, IL, USA). Statistical significance was assumed at $p < 0.05$.

Results

Sample characteristics

Of the 326 women that underwent routine screening and were asked to participate, 77 were excluded due to language problems and 25 declined to participate. Of the 224 participating women, 2 women were excluded in a second step due to their current medication intake, 9 due to medical problems and 10 for both reasons. The remaining 203 participants fulfilled all inclusion criteria and participated in the study. Of these participants, 39 (19.2%) were diagnosed with GDM. Two-hour glucose concentrations were missing for one, copeptin for seven, morning cortisol for six, and bedtime cortisol for 31 participants. Furthermore, 38 cases were missing for the amount of physical activity, 21 for gestational age, nine for current BMI, and one for sleep quantity. Finally, 19 cases did not provide enough information to calculate the 'number of pregnancy-unrelated major life events in the last 12 months'.

Baseline group data are shown in Table 1. Compared with women without GDM, women with GDM were significantly older ($t = 3.13$, $p = 0.002$, $g = .56$), had a significantly higher BMI before pregnancy ($t = 2.75$, $p = .006$, $g = .51$), and a significantly higher current BMI ($t = 2.66$, $p = .008$, $g = .52$). Both groups did not significantly differ in terms of gestational age, migrant and marital status, educational background, family history of diabetes, gestational diabetes mellitus in a previous pregnancy, total amount of sleep per night, and duration of physical activity per week (all $p \geq .16$).

Discussion

The results of our study should be considered in the context of some methodological limitations: (1) cortisol and copeptin were measured on one specific day only and not prior to glucose, (2) compliance to exact timing of evening cortisol sampling was not verified as all women took the second sample at home, (3) morning cortisol was measured at least 90 min after awakening and only twice and thus an exact circadian rhythm cannot be taken into account, (4) lack of consideration of dietary factors as potential confounders, , and (5) lack of measuring social support and coping, both of which are important protective factors against the negative effects of stress (Moos & Holahan, 2003; Ozbay et al., 2007).

Conflict of interest

The authors have no conflict of interest to disclose.

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Table 1: Sample characteristics according to presence or absence of gestational diabetes mellitus

	GDM n = 39	No GDM n = 164
Age (years)	32.73 ± 5.17	29.70 ± 5.50
Gestational age (weeks) [a]	26.14 ± 2.70	25.74 ± 2.07
Migrant status	29 (72.5)	134 (75.7)
Marital status		
Single	3 (7.7)	8 (4.9)
Couple	20 (51.3)	85 (51.8)
Single parent	2 (5.1)	6 (3.7)
Couple with child(ren)	14 (35.9)	65 (39.6)
Educational background		
Compulsory education* not completed	3 (7.7)	5 (3.0)
Compulsory education completed	9 (23.1)	45 (27.4)
Apprenticeship	11 (28.2)	38 (23.2)
Secondary school	1 (2.6)	15 (9.1)
University degree	15 (38.5)	61 (37.2)
Family history of diabetes	12 (30.8)	37 (22.6)
GDM in previous pregnancy	1 (2.6)	4 (2.4)
BMI before pregnancy (kg/m^2) [a]	25.15 ± 6.00	22.78 ± 4.29
Current BMI (kg/m^2) [a]	28.46 ± 6.14	26.04 ± 4.31
Sleep quality		

Very good	2 (5.1)	12 (7.3)
Fairly good	20 (51.3)	90 (54.9)
Fairly bad	14 (35.9)	55 (33.5)
Very bad	3 (7.7)	7 (4.3)
Total amount of sleep (min per night) [a]	470.24 ± 110.58	485.23 ± 90.64
Total amount of moderate to vigorous physical activity (min per week) [a]	36.92 ± 58.57	50.29 ± 80.02

GDM = gestational diabetes mellitus; BMI = Body Mass Index; *Compulsory education in Switzerland lasts for 9 years (usually between the ages of 6 and 15)
Data are shown as mean (SD) or n (%); Migrant status defined if born outside of Switzerland; [a] estimates for *M* and *SD* were based on a single data set imputed directly from EM parameters with NORM (Schafer, 1999).