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# Preconceptual leptin levels in gestational diabetes and hypertensive pregnancy

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**ABSTRACT**

Pregnancy – induced hypertension (PIH), preeclampsia (PE), and gestational diabetes (GDM) are common adverse outcomes in pregnancy.

**Objective:** To find out whether preconceptual leptin levels differ in subsequent pregnancy between control vs. GDM and hypertensive pregnancy groups.

**Materials and Methods:** Data was from The Cardiovascular Risk in Young Finns Study and The Medical Birth Register of Finland. Of 293 subjects 71 developed GDM, 27 PIH/PE and 201 were controls.

**Results:** Leptin was higher in GDM ($p < 0.0001$) and PIH/PE ($p = 0.0002$) groups compared to control. GDM group was robust to BMI matching (p = 0,0081).

**Conclusion:** Leptin was higher in GDM ($p < 0.0001$) and PIH/PE ($p = 0.0002$) groups compared to control. GDM group was robust to BMI matching (p = 0,0081).

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**KEYWORDS**
Gestational diabetes; pregnancy-induced hypertension; preeclampsia; leptin

## Introduction

Gestational diabetes mellitus and hypertensive pregnancy are the two most common pregnancy complications related to insulin resistance and sympathetic overactivity.

Definition of gestational diabetes mellitus (GDM) is "any degree of glucose intolerance with onset or first recognition during pregnancy" by American Diabetes Association. Approximately 19% of pregnancies in Finland are affected by GDM, and prevalence has increased during recent years. A meta-analysis shows that GDM predicts the development of type 2 diabetes mellitus (T2DM) in the mother later on (1). Furthermore, GDM increases the risk to adverse perinatal outcomes such as macrosomia, birth trauma, hypoglycemia, hyperbilirubinemia, and respiratory distress syndrome.

Pregnancy-induced hypertension (PIH) and preeclampsia (PE) are the most common hypertensive states in pregnancy. In Finland, 6–7% of pregnancies are hypertensive, and 2–3% pre-eclamptic. PIH is defined as a new hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) during or after 20$^{th}$ gestational week, and definition of PE is proteinuria within PIH. PE increases the risk to perinatal mortality when restricting the growth of a fetus (2). Furthermore, PIH and PE increase the risk to chronic hypertension (3), T2DM and cardiovascular diseases in the mother later on (4).

Leptin is a 16 kDa protein hormone, which plays a significant role in body weight regulation, energy expenditure and regulation of food intake (5) and is predominantly secreted by adipose tissue. Amount of fat mass seems to be the strongest predictor of circulating leptin (6). Moreover, placenta is known to be an additional source of leptin (7). Furthermore, circulating leptin levels correlate inversely with age in women when adjusted for BMI or fat mass percentage (6).

There is evidence that leptin concentrations are higher in individuals with metabolic syndrome (MetS) (8). In addition, leptin levels correlate positively with insulin resistance (9–11). It's been suggested that leptin stimulates central sympathetic activity (12) yet it's role in premenopausal women is believed not to be great (13,14).

Our hypothesis: preconceptual leptin levels are higher in GDM and hypertensive pregnancy developers when compared to healthy controls. Our objective was to find out whether preconceptual serum leptin levels as indirect marker of insulin resistance differed between control versus GDM and hypertensive pregnancy groups and whether it's related or independent to BMI. In the same way we studied whether other markers: high sensitivity C-reactive protein (hs-CRP), aspartate transaminase (AST), blood pressure (BP), and

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resting heart rate (RHR) – as indirect markers of low-grade inflammation, visceral fat and sympathetic activity – differed between cases and controls. Study design was nested case control.

## Materials and methods

Population and data of this study were extracted from The Cardiovascular Risk in Young Finns Study and the Medical Birth Register of Finland. The Cardiovascular Risk in Young Finns Study is a follow-up study aiming to determine childhood risk factors in common cardiovascular diseases. Its baseline study was arranged in 1980 and follow-ups after 3, 6, 9, 12, 21, 27, and 30 years from 1980. Participants' age range in the baseline was 3–18 years and number 3596. In 2001, which is the reference point for this study, there were 2283 subjects, aged 24–39 years, of which 1257 were women. Of those, 511 later experienced pregnancy, 6 of the pregnant got preeclampsia (PE), 29 got pregnancy-induced hypertension (PIH), and 82 gestational diabetes mellitus (GDM). Three-hundred and ninety-four didn't get gestational complications mentioned above.

From the Medical Birth Register of Finland we gathered the information whether women went through normal pregnancy, GDM, PIH, or PE. Data included pregnancies from the reference point to November 2015 for a total period of 14 years. To be noted, systematic collection of pregnancy complications started in 2003, yet there were few cases of GDM and PIH reported before 2003.

GDM group had 71 subjects after exclusion and included women who were diagnosed with GDM according the birth register after the measurement of 2001. The diagnosis was made, if plasma glucose (mmol/l) overlapped in one of three measure points in two-hour oral glucose test (75 g per os glucose): fasting 5.3, one-hour-point 10.0, and two-hour-point 8.6. All women with a diagnosis of diabetes and pregnant women at the measuring moment in 2001 were excluded from the GDM group as well. Mean BMI of the women in GDM group was 24,7 kg/m$^2$ (±SD 4.2) and mean age was 29 years (±SD 4.3).

PE/PIH group had 27 subjects after exclusion and included women who were diagnosed with PE or PIH or were treated in a hospital due to high blood pressure during pregnancy by the birth register after the measurement of 2001. Diagnostic criteria for PIH: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg during or after 20$^{th}$ gestational week. And for PE: same as PIH plus proteinuria. All women with a diagnosis of essential hypertension and pregnant women at the measuring moment in 2001 were excluded from the PE/PIH group. Group's mean BMI was 26.1 kg/m$^2$ (±SD 4,7) and mean age was 30 years (±SD 3.7). Six subjects had hypertensive pregnancy and GDM simultaneously.

BMI-matched control group for GDM had 142, for PE/PIH 54, and for PIH+GDM 12 subjects. Control groups included women, who did not have history of GDM, PIH, PE, fetal macrosomia (≥4000 g), pathological blood glucose level during pregnancy or high blood pressure treated in hospital during pregnancy in the pregnancy register after 2001. Pregnant women in 2001 and women diagnosed with essential hypertension were excluded as well.

Control group had 201 subjects, and exclusion criteria were similar to other groups. Mean BMI was 22,6 kg/m$^2$ (±SD 3.5), and mean age was 28 years (±SD 3.8).

The groups are presented in Figure 1 and parameters studied of each group in Table 1.

Subjects fasted for 12 hours before the blood samples, which were drawn generally between 7 am and 11 am. Serum was separated from the samples and stored at −70°C until analysis.

Measurements of leptin were accomplished at the laboratory of the Department of Pharmacology, Drug Development and Therapeutics, University of Turku, Turku. Leptin concentrations in serum were determined by a radioimmunoassay method (Human Leptin RIA kit, Linco Research, Inc., MO, USA). The inter-assay coefficient of variation was 7–9%. Concentration unit was ng/mL.

Measurements of hs-CRP were accomplished at the laboratory of the Research and Development Unit of the Social Insurance Institution, Turku. CRP concentrations in serum were determined by a high-sensitive latex turbidometric immunoassay method (Wako Chemicals GmbH, Neuss, Germany). Assay's detection limit was 0.06 mg/L, and the coefficient of variation of repeated measurements was 3.3%.

Measurements of AST were accomplished at the Department of Laboratory Medicine, Konventhospital Barmherzige Brueder Linz, Austria. AST concentrations in serum were measured on an ARCHITECT automated analyzer (Abbott Diagnostics, Abbott Parks, IL, USA). Concentration unit was U/L.

Blood pressure and resting heart rate were measured after 15 minutes of restby using mercury manometer and calculating three-time average.

### Statistical methods

Square root transformations were made to leptin and AST, and log transformations to hs-CRP and resting heart comparisons because of skewed data. BP was

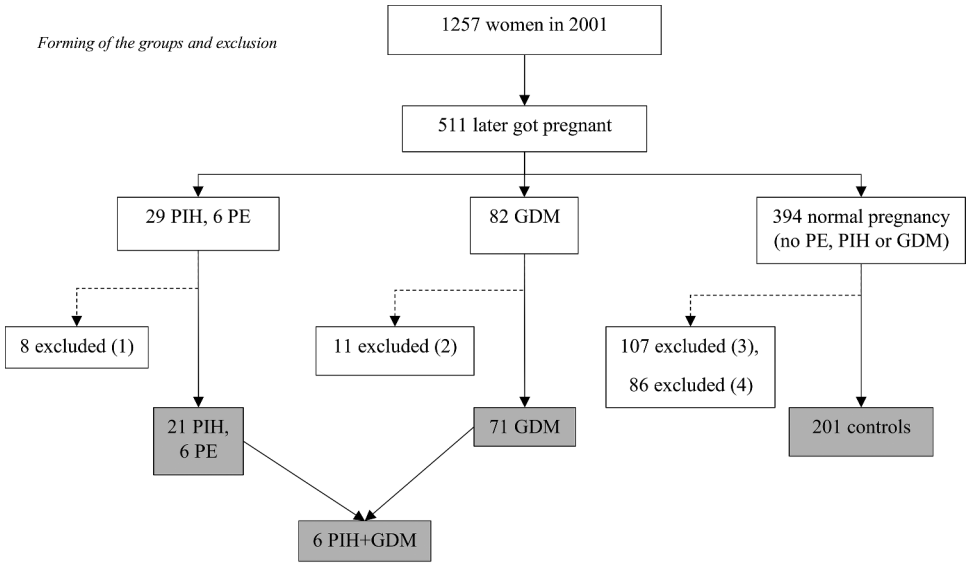


**Figure 1.** Forming of the groups and exclusion.

**Table 1.** Characteristics and statistical analyses.

| | *Characteristics* | | | |
|---|---|---|---|---|
| | *Group* | | | |
| | Control | GDM | PIH/PE | PIH+GDM |
| *n* | 201 | 71 | 27 | 6 |
| BMI – kg/m$^2$ | 22.6 (17.7–43.1; 3,.5) | 24.7 (17.6–37.2; 4.2) | 26.1 (18.8–36.4; 4,7) | 25.2 (22.0–31,.0; 3.2) |
| age – years | 28 (24–39; 3.8) | 29 (24–39; 4.3) | 30 (24–36; 3.7) | 30 (24–33; 3.5) |
| leptin – ng/mL | 11.5 (7.5–15.4) | 16.4 (10.2–24.2) | 16.4 (11.2–24) | 16.1 (13.0–20.9) |
| hs-CRP – mg/L | 0.68 (0.34–1.50) | 1.04 (0.36–1.93) | 0.67 (0.38–2.05) | 1.2 (0.22–1.52) |
| AST – U/L | 15.0 (13.0–18.0) | 15.0 (13.0–19.0) | 15.0 (13.0–19.0) | 16.5. (13.0–19.0) |
| RHR – 1/min | 66.7 (61.3–72.0) | 68.3 (64.0–74.0) | 68.0 (62.0–74.7) | 74.5 (68.0–75.3) |
| SBP – mmHg | 111.2 (84.7–145.3; 11.3) | 112.0 (88.0–134.0; 10.5) | 119.5 (94.7–166.7;16.2) | 121.9 (112.7–132.7; 8.7) |
| DBP – mmHg | 66.6 (42.7–95.3; 9.8) | 68.1 (50.7–89.3; 8.4) | 75.0 (58.0–108.7; 12.3) | 79.6 (72.7–89.3; 6.5) |

BMI, age, SBP, and DBP: mean (min–max; ±SD)
Leptin, hs-CRP, AST, and RHR: median (1. quartile - 3. quartile)

*Statistical comparisons to controls in unmatched model*

| | *Group* | | |
|---|---|---|---|
| Variable | GDM | PIH/PE | PIH+GDM |
| Leptin | <0.0001 | 0.0002 | 0.024 |
| hs-CRP | 0.094 | 0.58 | 0.76 |
| AST | 0.72 | 0.8 | 0.67 |
| RHR | 0.11 | 0.079 | 0.079 |
| SBP | 0.63 | 0.0005 | 0.023 |
| DBP | 0.27 | <0.0001 | 0.0015 |

Bolded statistically significant *p*-values

*Statistical comparisons to controls in BMI-matched model*

| | *Group* | | |
|---|---|---|---|
| Variable | GDM | PIH/PE | PIH+GDM |
| leptin | 0.0081 | 0.89 | 0.12 |
| hs-CRP | 0.45 | 0.34 | 0.48 |
| AST | 0.7 | 0.83 | 0.4 |
| RHR | 0.091 | 0.47 | 0.0087 |
| SBP | 0.96 | 0.08 | 0.029 |
| DBP | 0.43 | 0.04 | 0.012 |

Bolded statistically significant *p*-values.

normally distributed so there was no need for transformations in systolic or diastolic blood pressure analyses. We had three case groups: GDM, PIH/PE, and PIH +GDM, which each were compared by all of the six parameters mentioned above to two different control groups: all controls ($n$ = 201) and BMI-matched control group, in which the number of subjects were two times the case group. Statistical comparisons between case groups and control groups were done by using One Way ANOVA. Odds ratios of GDM in BMI-matched model were calculated by logistic regression. In BMI-matched model of GDM Correlation coefficients of leptin vs RHR were calculated by Spearman. In the same model, after dividing leptin to tertiles, RHR mean values between tertile groups were compared by Tukey-Kramer test.

All the statistical analyses were performed by using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

## Results

Power analyses indicated that 27 subjects per group were needed to provide 80% power to detect 7.5 mean difference between the two groups (using One Way ANOVA and two-tailed alpha of .05). Mean difference is similar to that in the article Maternal Circulating Concentrations of Tumor Necrosis Factor-Alpha, Leptin, and Adiponectin in Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis (15). Thus, our sample size is sufficient.

When all 201 controls were compared with GDM, PIH/PE and PIH+GDM groups, leptin levels were significantly different in GDM ($p$ < 0.0001), PIH/PE ($p$ = 0.0002), and PIH+GDM ($p$ = 0.024) groups. Systolic blood pressure (SBP) differed in PIH/PE and PIH+GDM groups ($p$ = 0.0005 and 0,.023 respectively), and diastolic (DBP) differed as well ($p$ < 0.0001 and 0.0015, respectively). Hs-CRP, AST and HR didn't differ significantly. Results are shown in Table 1 and box plot chart of leptin in Figure 2.

After matching for BMI, leptin levels between GDM and control group remained significantly different ($p$ = 0.0081). CRP, AST, RHR, and BP levels didn't differ significantly between GDM and control group in BMI-matched model. SBP difference remained significant in PIH+GDM group ($p$ = 0.029), and DBP in PIH/PE and PIH+GDM groups ($p$ = 0.04 and 0.012, respectively) in BMI-matched model. Leptin, CRP, AST, and RHR didn't have a statistically significant difference between PIH/PE and control group nor between PIH+GDM and control group in BMI-matched model except for there was a significant difference in RHR between PIH+GDM and matched control group ($p$ = 0.0087). Results are illustrated in Table 1, and leptin distribution in Figure 2.

In addition, we divided BMI-matched model of GDM in tertiles and quartiles by leptin values, and monitored OR of upper tertile and quartile to rest of the tertiles and quartiles, which were fused together. Odds ratio of GDM in BMI-matched model was 2.38 (95%Cl: 1.31–4.31), when upper tertile was compared to the rest of the two tertiles. After we compared upper quartile to the rest of the three quartiles OR was 3.05 (95%Cl: 1.60–5.80). The results are shown in Table 2.

At last, we figured, whether leptin and RHR had correlation. We fused GDM group ($n$ = 71) and BMI-matched control group for GDM ($n$ = 142), and monitored the correlation between leptin and RHR. As a result, there was a statistically significant correlation between leptin and RHR (Spearman correlation = 0.17; $p$ = 0.014). After dividing leptin to tertiles, RHR mean

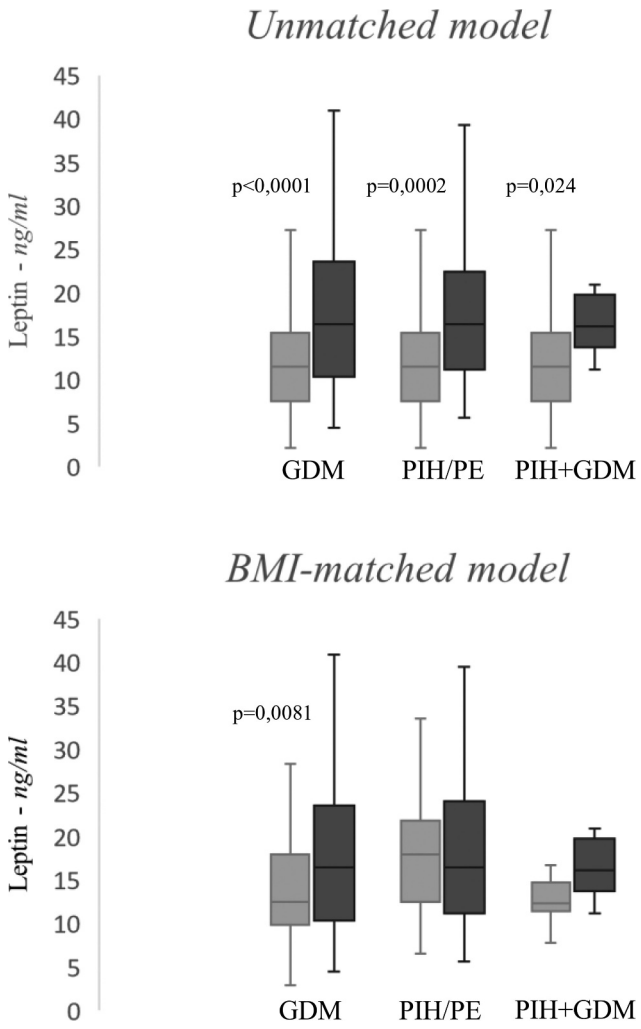


**Figure 2.** Box plot charts of leptin in unmatched and BMI-matched models.

in upper tertile was significantly higher (p = 0.033), when compared to the lowest tertile. There were no significant differences between other tertiles. Mean BMI values in RHR formed tertiles were 24.4 (±SD 3.4) in 1st, 23.7 (±SD 3.7) in 2nd and 24.3 (±SD 3.8) in 3rd.

Spearman correlations alone in GDM and BMI-matched control group were 0.049 ($p$ = 0.69) and 0.20 ($p$ = 0.015), respectively.

## Discussion

Main results of our study are:

(1) Leptin levels compared to BMI-unmatched controls in GDM and hypertensive pregnancy groups were elevated – before the onset of the pregnancy.
(2) GDM group's leptin levels were also elevated in BMI-matched model. OR of GDM in BMI-matched model was 3.05 (95%Cl: 1.60–5.80), when upper leptin quartile was compared to rest of the quartiles.

Side results of the study:

(1) Leptin correlated positively ($p$ = 0,020) with RHR in healthy control group (BMI-matched control for GDM), yet correlation wasn't significant in GDM group.
(2) Leptin in highly complicated pregnancy (GDM and PIH simultaneously) differed in unmatched model.
(3) RHR in highly complicated pregnancy differed in BMI-matched model, yet not in unmatched model.
(4) SBP and DBP in highly complicated pregnancy differed in both unmatched and BMI-matched model.
(5) DBP in PIH/PE differed in both unmatched and BMI-matched model.
(6) SBP differed in PIH/PE differed in unmatched model, yet difference vanished in BMI-matched model.

**Table 2.** GDM incidence in leptin formed quartiles and tertiles, BMI-matched model.

| | *Tertiles* | |
|---|---|---|
| | Tertiles 1–2 | Tertile 3 |
| GDM | 38 | 33 |
| control | 104 | 38 |
| OR | Reference | 2.38 (95%Cl: 1.31–4.31) |
| | *Quartiles* | |
| | Quartiles 1–3 | Quartile 4 |
| GDM | 43 | 28 |
| control | 117 | 25 |
| OR | Reference | 3.05 (95%Cl: 1.60–5.80) |

Increased leptin concentrations have been associated with GDM in a meta-analysis of 27 studies, which found that leptin levels in late second or third trimester were significantly higher in women who developed GDM when compared to controls. After adjusting for BMI, findings remained similar (15). One study found that elevated leptin levels, independent of BMI, in early pregnancy (<16 weeks) predicted the development of GDM later in the pregnancy (16). A small prospective study of 15 subjects revealed that women who developed GDM had decreased insulin sensitivity a couple of months before conception compared to controls (17), and in addition to that, bearing in mind leptin's positive correlation with insulin resistance (9–11), leptin can be considered as an indirect mark of insulin resistance. Thus, elevated concentrations of leptin in association with subsequent GDM, which our study suggested, might be explained at least partly by increased insulin resistance. Furthermore, considering a recent prospective study, which suggests nonalcoholic fatty liver disease as an independent risk factor for GDM (18), and, in addition, according to a meta-analysis leptin levels were elevated in patients with fatty liver disease when compared to controls and associated with severity of nonalcoholic fatty liver disease (NAFLD) (19). It's possible that part of our subjects developed GDM due to underlying NAFLD, of which early marker leptin might be, yet our results can't confirm that due to lack of NAFLD related data.

When it comes to preconceptual leptin levels, our study added new information: Elevated preconceptual leptin levels, even normalized with BMI seem to increase the risk of subsequent GDM, which supports the conception that leptin is an indirect marker of insulin resistance (9–11). Leptin levels were also elevated in women, who developed hypertensive pregnancy, yet BMI normalization led the levels not to differ significantly, which is evidently explained by leptin's strongest predictor amount of fat mass (6).

A prospective study revealed that hs-CRP levels correlated positively with plasma glucose levels in pregnant women, after adjustment for BMI and C-peptide (20). Another prospective study found as well that risen hs-CRP levels predicted GDM later in pregnancy when measured before the 15th gestational week (21). We didn't find longer-term associations with hs-CRP and GDM.

A meta-analysis of 23 studies showed that CRP evaluation in early pregnancy may predict preeclampsia (22). In

contrast to that we didn't find association between hs-CRP and hypertensive pregnancy, when measured years before the onset of the pregnancy. To be noted, our hypertensive group included just six pre-eclamptic developers, which possibly may affect the result.

AST has not been linked to GDM by a prospective study, when measured antenatally (23). Pre-gravid AST levels didn't associate with GDM in subsequent pregnancies by a retrospective study (24). Our study suggested parallel results by not finding long term associations between AST concentration and future GDM.

Associations with AST and PIH haven't been studied that much. However, a retrospective study, including 15,010 births, found an association between severe PE and AST concentrations over AST's reference range, yet there was no significant difference in reference range exceeding AST levels between mild PE and normotensive control subjects (25). Our results didn't found association between AST levels and subsequent hypertensive pregnancy nor GDM.

Mendoza et al. (26) reported higher RHR in pregnant women at <28 gestational weeks as a risk factor for GDM. Our study didn't find association between pre-pregnancy measured RHR and GDM. Resting heart rate could indicate, although not as a perfect indicator, sympathetic activity especially at heart level. Increased central sympathetic activity as an inducer of increased insulin resistance, seems to prevail after pre-eclamptic pregnancy (27). Positive correlation between resting heart rate and circulating leptin, independent of BMI, have been demonstrated in a study consisting of 2264 males and 2545 females (28). Our results were similar as we found an interesting, yet mild correlation between leptin and RHR in our healthy subjects (Spearman correlation = 0.20; $p = 0.015$) To be noted, correlation wasn't significant in GDM group (Spearman correlation = 0.049; $p = 0.69$), due to which leptin's inducing effect on RHR and sympathetic activity in association with subsequent GDM cannot be claimed by our results. This raises the question whether individuals with subsequent GDM, had suppressed leptin's impact on RHR.

Higher preconception BP has been identified as a risk factor for PIH and PE in earlier studies (29,30). Our results were in line with that as we found SBP and DBP remained different in PIH+GDM group, and DBP in PIH/PE group despite BMI-matching. In unmatched model there was also difference in PIH/PE group between DBP levels (see Table 1). These results reinforces the perception that pre-gravid blood pressure monitoring might help to determine individuals, who are at the risk for hypertensive disorders of pregnancy.

As other side results, leptin concentrations in unmatched model differed between control and PIH +GDM ($p = 0.024$), yet the association vanished after matching for BMI ($p = 0.12$). Similar tendency was seen in PIH/PE group where BMI-matching led to an increase in $p$ value from 0.0002 to 0.89. Furthermore, PIH+GDM group's RHR differed from matched control. Surprisingly, in unmatched model there was no difference. These somehow conflicting results probably can be explained by remarkably small cohort of PIH +GDM. Thus, when it comes to highly complicated pregnancy (PIH+GDM), robust conclusions cannot be made by our study.

Nested case-control design is one weakness of this study. To get more reliable results, well planned prospective design with hypothesis from our claimed results would give more robust conclusion. In addition, we used BMI as a marker for adipose tissue's mass, which necessarily doesn't monitor correctly the amount of adipose tissue in every subject. Furthermore, restrictions of the Medical Birth Register of Finland can be also count as a frailty: diagnoses of pregnancies have been gathered since 2003, which causes that there is no information about PIH, PE or GDM in previous pregnancies of subjects. However, few cases of GDM and PIH were reported before 2003, yet systematic collection of the data of pregnancy complications started in 2003. To be noted, leptin analyses were made from frozen plasma, which leads to decreased leptin concentration due to protein fragmentation. Storing times were reasonably similar due to which leptin concentrations were comparable between our subjects. Furthermore, control population of our study has been selected to minimize major confounding factors of leptin, such as BMI and pregnancy status. Thus, the controls might include major lurking variables for AST, CRP, BP, and RHR, which haven't been taken into account.

## Conclusion

As novelty, our study suggested that higher preconceptual leptin levels might be a risk factor for GDM independently of BMI, and for hypertensive pregnancy BMI dependently. Leptin might be an indirect marker for insulin resistance, which contributes to development of subsequent GDM. According to our results leptin seems to be an indirect marker of BMI, which, not itself is causal yet strongly correlates with the adipose tissue's mass that directly affects blood pressure when it comes to hypertensive states of pregnancy. Our study also reinforced the earlier

perception that pre-gravid BP monitoring might help to identify patients who are at risk for hypertensive pregnancy. Furthermore, our study revealed significant positive correlation with leptin and RHR in healthy subjects. Therefore, screening leptin concentrations might help to determine individuals who are at risk for GDM later on.

## Disclosure statement

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