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Prediction of Gestational Diabetes and Hypertensive Pregnancy by serum Leptin, C-Reactive Protein, Aspartate Transaminase levels, and Resting Heart Rate

Syventävien opintojen kirjallinen työ

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Tiivistelmä

Leptiini, C-reaktiivinen proteiini, aspartaatti transaminaasi ja leposyke ennen raskausdiabetesta ja hypertensiivistä raskausta

Raskausdiabetes, pre-eklampsia ja raskauden aikainen verenpaineen nousu ovat yleisiä raskauteen liittyviä komplikaatioita, joilla on vaikutusta synnyttävän äidin sekä syntyneen sikiön sairastuvuuteen sekä myöhemmällä iällä, että diagnoosivaiheessa.

Tutkimuksen tarkoituksena oli vertailla seerumin leptiinin, herkän C-reaktiivisen proteiinin (hs-CRP), aspartaatti transaminaasin (ASAT) ja leposykkeen eroja ennen raskauksia ja vertailla näitä terveisiin, normaalin raskauden läpikäyneisiin kyseisten muuttujien osalta.

Tämän tutkimuksen aineisto kerättiin lasten sepelvaltimotaudin riskitekijät -tutkimuksesta ja syntyneiden lasten rekisteristä. Yhteensä tässä tutkimuksessa oli 511 naista, joista otettiin näytteitä vuonna 2001, ja jotka myöhemmin tulivat raskaaksi. Seuranta-aika oli 14 vuotta. Poissulkukriteereiden jälkeen tarkasteltavaksi jäi 71 raskausdiabetekseen, 21 raskauden aikaiseen verenpaineen nousuun ja pre-eklampsiaan sairastunutta. 201 oli normaalin raskauden läpikäyneitä kontrolleja.

Leptiinitasot olivat tilastollisesti korkeammat naisilla, jotka myöhemmin kehittivät raskausdiabeteksen 16,4 *ng/ml* (IQR: 10,2-24,2) ($p<0,0001$) tai hypertensiivisen raskauden 16,4 *ng/ml* (IQR: 11,2-24) ($p=0,0002$) (pre-eklampsia tai raskauden aikainen verepaineen nousu) verrattuna kontrolliiryhmään 11,5 *ng/ml* (IQR: 7,5-15,4). Tilastollinen merkittävyys säilyi raskausdiabeteksen osalta painoindeksikaltaistamisen jälkeen. Ylimmässä leptiinikvartaalissa OR (”odds ratio”) raskausdiabeteksen suhteen oli 3,05 (95%CI: 1,60-5,80), kun sitä verrattiin kaikkiin muihin kolmeen alimpaan kvartaaliin. Tertiilien suhteen vastaava OR oli 2,38 (95%CI: 1,31-4,31). Hs-CRP, ASAT ja leposyke ei ollut yhteydessä myöhempään raskausdiabetekseen tai hypertensiiviseen raskauteen.

Tulosten perusteella korkea seerumin leptiinipitoisuus on yhteydessä myöhempään raskausdiabetekseen BMI-riippumattomasti. Korkea leptiinipitoisuus liittyy myös myöhempään hypertensiiviseen raskauteen, kun BMI:tä ei oteta huomioon. Seerumin leptiinikonsentraation mittaamisesta voi olla hyötyä raskausdiabeteksen riskiryhmään kuuluvien naisten määrittämisessä.

Prediction of Gestational Diabetes and Hypertensive Pregnancy by serum Leptin, C-Reactive Protein, Aspartate Transaminase levels, and Resting Heart Rate

Peltokorpi A, Lisinen I, Viikari L, Kaaja R

Abstract

Hypertensive pregnancy including pregnancy-induced hypertension (PIH), preeclampsia (PE) and gestational diabetes (GDM) are common adverse outcomes related to insulin resistance in pregnancy.

Objective: To find out, whether factors related to insulin resistance leptin, high-sensitivity C-reactive protein (hs-CRP), aspartate transaminase (AST) and resting heart rate (RHR) could predict hypertensive pregnancy and GDM later in woman´s life.

Material and methods: In this nested case-control study the data was obtained from The Cardiovascular Risk in Young Finns Study and The Medical Birth Register of Finland. Altogether, 1257 women, aged 24-39 years, were included in this study. They gave blood samples and arranged to measurement of RHR in 2001. Of these 1257 women 511 later became pregnant. Follow-up time was 14 years up to November 2015. Women who were pregnant at the moment of the blood sampling were excluded initially. The final research material consisted of 293 women, of whom 71 developed GDM, 21 PIH, 6 PE and 201 were controls, who experienced normal pregnancy. Six women had a pregnancy with GDM and PIH.

Results: Serum leptin levels were higher in women who developed gestational diabetes or hypertensive pregnancy later on: serum leptin 16,4 *ng/ml* (IQR: 10,2-24,2), 16,4 *ng/ml* (IQR: 11,2-24) respectively compared to control women 11,5 *ng/ml* (IQR: 7,5-15,4), p<0.0001 and 0,0002). After matching for BMI, difference remained significant in GDM group (p=0,0081) yet not in PIH/PE group (p=0,89). OR of GDM in upper leptin quartile compared to rest of quatiles was 3,05 (95%CI: 1,60-5,80). In other markers (hs-CRP, AST and RHR) there were no statistically significant differences between control and PIH/PE or GDM group in BMI-matched, and unmatched models

Conclusion: High serum leptin levels predicted gestational diabetes independent of BMI. Elevated leptin levels were also associated with hypertensive pregnancies, however, the association vanished after adjusting for BMI. Hs-CRP, AST nor resting heart rate did not associate with development of hypertensive pregnancy or GDM.

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 20th 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 16kDa 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 of that leptin concentrations are higher in individuals with metabolic syndrome (MetS) (8). In addition, leptin levels correlate positively with insulin resistance (9,10,11). 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).

C-reactive protein (CRP) is generally known as an acute phase protein, synthetized by hepatocytes, of which concentration in blood highly elevates during infection- and tissue damage. On the other hand, high sensitivity CRP (hs-CRP) concentration, as a marker of low-grade inflammation, correlates positively with BMI and obesity (15). Increased hs-CRP levels have been linked to MetS (25). Moreover, increased hs-CRP levels in women predict the development of hypertension and atherosclerosis (16).

Aspartate transaminase (AST) is an important enzyme in amino acid metabolism, which is found in the liver, heart, kidneys, skeletal muscles, red blood cells, and brain. Generally, high serum AST

concentrations have been linked with a fatty liver disease, and visceral adipose tissue's mass is positively related to AST levels in overweight people (17).

Resting heart rate (RHR) is an unsensitive indicator of sympathetic nervous system activity. It correlates with the activity of muscle sympathetic nerves and plasma norepinephrine concentrations (18).

Our objective: was to find out, whether serum leptin, hs-CRP, AST levels and RHR as indirect markers of insulin resistance, low-grade inflammation, visceral fat and sympathetic activity could predict the development of GDM and hypertensive pregnancy (PIH or PE) later in mother's life and whether these factors are independent or related to BMI.

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. Participant's age range in the baseline was 3-18 years and number 3596. In 2001, which is the reference follow-up 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.

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 (75g 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 24,7kg/m2 (±SD 4,2) and mean age was 29 years (±SD 4,3).

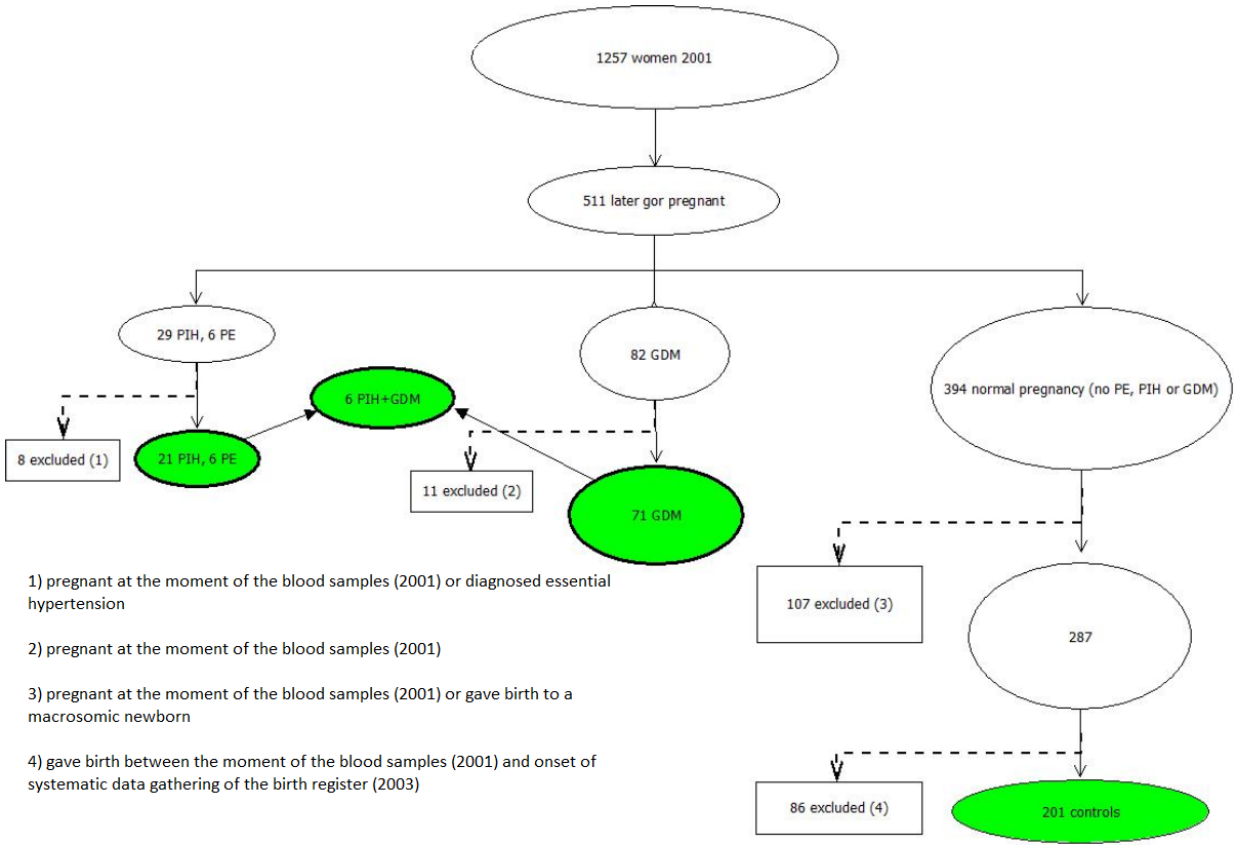
PE/PIH group had 27 subjects after exclusion and included women who were diagnosed with PE or PIH or were treated in a hospital due to high blood pressure during pregnancy by the birth register after the measurement of 2001. Diagnostic criteria for PIH: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg during or after 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 26,1kg/m2 (±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 (≥4000g), 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/m2 (±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.

Figure 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.

Resting heart rate per minute was measured after 15 minutes of rest, together with blood pressure analysis by 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. We had three case groups: GDM, PIH/PE, and PIH+GDM, which each were compared by all of the four 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

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. Hs-CRP, AST and HR didn't differ significantly.

Results are shown in table 1.

Table1

	control	GDM	PIH/PE	PIH+GDM
n	201	71	27	6
BMI - *kg/m2*	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) *
	p-value	<0,0001	0,0002	0,024
	p-value (BMI-matched)	0,0081	0,89	0,12
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) *
	p-value	0,094	0,58	0,76
	p-value (BMI-matched)	0,45	0,34	0,48
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) *
	p-value	0,72	0,8	0,67
	p-value (BMI-matched)	0,7	0,83	0,4
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) *
	p-value	0,11	0,079	0,079
	p-value (BMI-matched)	0,091	0,47	0,0087

BMI and age: mean (min – max; ±SD)

*Leptin, hs-CRP, AST and RHR: median (1. quartile - 3. quartile)

Table 1: Baseline patient characteristics (2001) and laboratory parameters (leptin, hs-CRP, AST and RHR) depending on clinical outcome: GDM, PIH/PE or PIH+GDM and in controls (all and BMI matched)

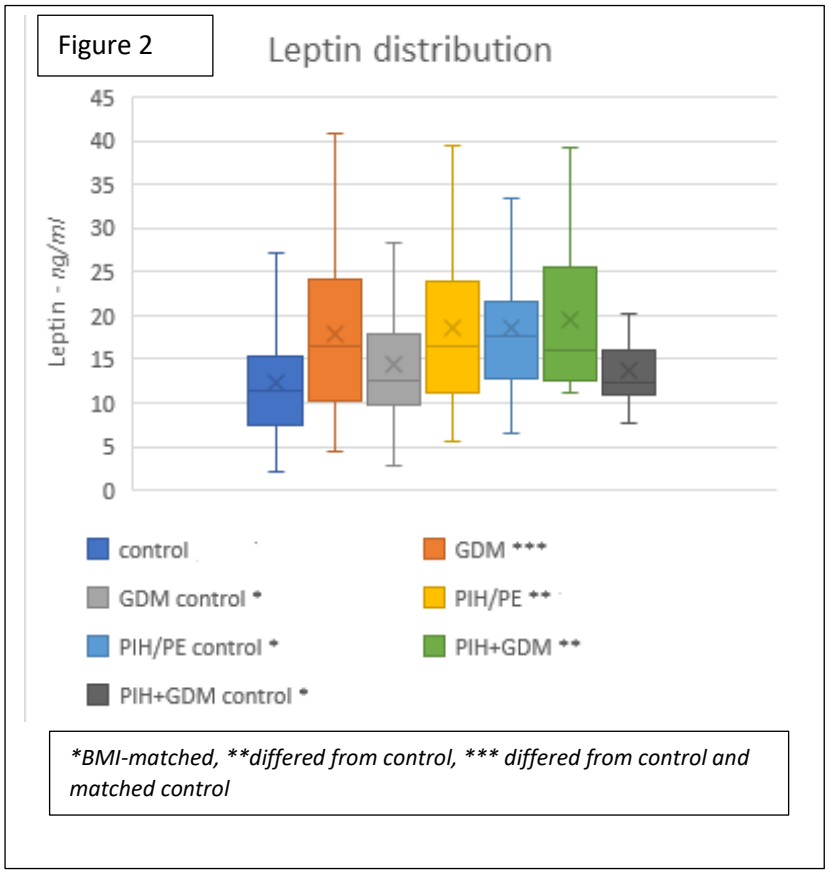


Figure 2: Leptin distribution of different groups. Median, mean (X) and quartiles are presented.

After matching for BMI, leptin levels between GDM and control group remained significantly different (p=0,0081). CRP, AST and RHR levels didn't differ significantly between GDM and control group in BMI-matched model. Leptin, CRP, AST, and RHR didn't have a statistically significant difference between PIH/PE and control group nor between GDM and control group in BMI-matched model. However, there was a significant difference in RHR between PIH+GDM and matched control group (p=0,0087).

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).

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 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 control in GDM and hypertensive pregnancy groups were elevated - before the onset of the pregnancy.
2. GDM group's leptin levels were 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.

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 (19). One study found that elevated leptin levels, independent of BMI, in early pregnancy (<16 weeks) predicted the development of GDM later in the pregnancy (20). A small prospective study of 15 subjects revealed that women who developed GDM had decreased insulin sensitivity couple of months before conception compared to controls (21), and in addition to that, bearing in mind leptin's positive correlation with insulin resistance (9,10,11), 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 non-alcoholic fatty liver disease as an independent risk factor for GDM (22), 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 non-alcoholic fatty liver disease (NAFLD) (23). 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.

A prospective study revealed that hs-CRP levels correlated positively with plasma glucose levels in pregnant women, after adjustment for BMI and C-peptide (27). Another prospective study found as well that risen hs-CRP levels predicted GDM later in pregnancy when measured before the 15th gestational week (28). 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 (29). 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 6 pre-eclamptic developers, which possibly may affect the result.

AST has not been linked to GDM by a prospective study, when measured antenatally (30). Pre-gravid AST levels didn't associate with GDM in subsequent pregnancies by a retrospective study (31). 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 (32). Our results didn't found association between AST levels and subsequent hypertensive pregnancy nor GDM.

Mendoza et al. (33) 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 (34). 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 (35). 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.

As 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 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 and RHR which haven't been taken into account.

Conclusion

Our study suggested that higher 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. Furthermore, our study revealed significant positive correlation with leptin and RHR in healthy subjects. Screening leptin concentrations might help to determine individuals who are at risk for GDM later on.

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