BMI: new aspects of a classical risk factor for hypertensive disorders in pregnancy

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ABSTRACT

HDP (hypertensive diseases in pregnancy) are one of the leading causes of maternal and fetal mortality and morbidity. BMI (body mass index) is an established risk factor for pre-eclampsia, but its role in HELLP syndrome is unknown. We therefore investigated BMI as a risk factor in the development of HELLP syndrome. At the beginning of pregnancy, BMI was measured in 1067 women with a history of HDP and 1063 controls. Diagnoses of HDP were classified according to ISSHP (International Society for the Study of Hypertension in Pregnancy) and BMI according to WHO (World Health Organization) criteria. After verification of exclusion criteria and matching for confounders, 687 women with hypertensive diseases in pregnancy and 601 controls remained for statistical evaluation by χ2 test and multiple logistic regressions. As a continuous variable, the increase in BMI was associated with an increase in the development of gestational hypertension {OR (odds ratio), 1.1 [95 % CI (confidence interval) 1.062–1.197]} and pre-eclampsia [OR, 1.1 (95 % CI, 1.055–1.144)], but not for HELLP syndrome. According to WHO definitions, overweight women (BMI ≥ 25 and < 30 kg/m2) had a 2-fold (95 % CI, 1.365–2.983) risk and obese women (BMI ≥ 30 kg/m2) had a 3.2-fold (95 % CI, 1.7–5.909) risk of developing pre-eclampsia when compared with women of normal weight (BMI ≥ 15.5 and < 25 kg/m2). Being overweight or having obesity had no effect on the risk of HELLP syndrome. As an increased BMI is correlated with the risk of developing pre-eclampsia but not HELLP syndrome, both diseases have a different risk profile. This finding supports that underlying physiological mechanisms in pre-eclampsia vary from those in HELLP syndrome.

INTRODUCTION

The prevalence of obesity is increasing worldwide and across all age groups [1,2]. In Germany, the prevalence of obesity [BMI (body mass index) ≥ 30 kg/m2] in women is between 21.1 and 24.5 %, and more than half of all women are overweight (BMI ≥ 25 and < 30 kg/m2) [3]. Being overweight has been associated with an increased rate of obstetric complications and poor neonatal outcomes. Women with a BMI ≥ 25 kg/m2 suffer significantly more often from gestational diabetes [4–6]. Their children are more often macrosomic [4,6], but other studies also report higher incidences of fetal growth restriction [7]. Being overweight is correlated with a dose-dependent increase in the risks of stillbirth and very preterm birth (<32 weeks) [4,5]. Overweight women have an

Key words: body mass index (BMI), gestational hypertension, HELLP syndrome, hypertensive disease in pregnancy, obesity, overweight, pre-eclampsia.

Abbreviations: BMI, body mass index; BP, blood pressure; CH, chronic hypertension; CI, confidence interval; GH, gestational hypertension; HELLP, HELLP syndrome; HDP, hypertensive diseases in pregnancy; OR, odds ratio; PE, pre-eclampsia; WHO, World Health Organization.

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augmented risk of delivery by Caesarean section [4–6],
post-operative morbidity [7] and treatment of their
children in a neonatal intensive care unit [4]. When
the mother's BMI is > 30 kg/m², the risk of fetal mal-
formation increases from 4–7 % to 11.1 % [8].

Being overweight and having obesity are also asso-
ciated with an increased risk of HDP (hypertensive
diseases in pregnancy) [4,6]. HDP are one of the main
reasons for maternal death in the U.S.A. and Europe
[9,10]. These diseases are responsible for approx. 15–
20 % of premature deliveries and perinatal death [11].
HELLP (HELLP syndrome) is often interpreted as a
severe form of PE (pre-eclampsia) [12,13], and it is corre-
LATED with an increased risk of maternal and fetal
morbidity and mortality [14]. Despite intensive research
and promising results, an integrated aetiological model of
HDP has not been formulated. Termination of pregnancy
is the only causal treatment available for HDP. Therefore
the prediction of risk or identification of subclinical
disease is desirable to identify patients who require
increased observation. Currently, patients at risk are dif-
ficult to recognize. Increased body weight is one of the
earliest known risk factors for HDP; however, its role
in HELLP remains unknown. Such a comparison may
help to understand the underlying pathophysiological
mechanisms, and knowledge of these mechanisms may
offer new opportunities for a causal treatment of these
diseases. Furthermore, weight reduction seems to be
a potential prophylactic option to reduce the risk of
PE, in contrast with most of the other known risk factors [15]. The correlation between pre-pregnancy
BMI and the risk for PE and HELLP is also of parti-
cular interest, as emerging data suggest associations
between the influence of maternal and fetal factors during
intrauterine growth and the risk of developing adult
obesity and its comorbidities [16]. Therefore the aim
of our present study was to investigate the role of pre-
pregnancy BMI in PE and HELLP.

MATERIALS AND METHODS

The Hy-Di-Preg study (Hypertensive Disorders in
Pregnancy) is a nationwide research project initiated
to investigate the role of epidemiological, psychosocial,
psychosomatic and genetic factors in the aetiology
and course of HDP. The project was designed in co-
operation with the German pre-eclampsia self-help group
(Arbeitsgemeinschaft Gestose-Frauen e.V.).

From the current literature and the clinical experience
of the authors, a standardized questionnaire focused on
the objectives of the study was developed. In addition,
medical records of each patient were reviewed for relevant
data. Questionnaires were sent to 2600 women who asked
the German Pre-Eclampsia Society for information on
HDP. Of the 2600 women contacted, 168 respondents
were professionals, such as physicians, nurses or mid-
wives. We received completed questionnaires from 1067 women who had had at least one episode of HDP.
Women also contacted the pre-eclampsia self-help group
when hypertensive disease was suspected, but could be
excluded by medical evaluation. Therefore the exact
response rate of women who had actually had HDP
could not be calculated. As gestational diabetes mellitus
and obesity seem to be dependent risk factors for preg-
nancy-induced hypertensive disorders [17], women with
diabetes were excluded from the study.

The control group was recruited from seven hospitals
in mid-west Germany. Women were excluded if they
presented with HDP, CH (chronic hypertension), a BP
(blood pressure) ≥ 140/90 mmHg more than once during
pregnancy, hypo- or hyper-thyroidism, gestational dia-
betes, diabetes mellitus, autoimmune diseases and/or
proteinuria > 0.3 g/l in a 24-h urine sample or > 1g/l
in a spontaneous urine sample (≥ 1+ on urine dipstick)
during pregnancy based upon medical record review.

After exclusion, 1484 control women were included in
the study. The questionnaire was then handed out and
1233 women agreed to participate. Lack of time was
the main reason (92 %) for not participating in the
study. We received 1063 completed questionnaires of
which 162 were excluded due to incomplete data sets.
No statistically significant differences existed between
the women participating or refusing to participate/being
excluded from the control group because of age, parity
or socio-economic status.

All participants provided written informed consent.
The study was approved by our Institution’s Ethics
Committee.

Patients and controls were only included when the
complete data set on main outcomes and potential con-
founders were available. The index pregnancy was de-
defined as the first pregnancy conducted beyond the 24th
week of gestation. In the cases, the first pregnancy
conducted beyond the 24th week of gestation and
complicated by HDP was considered for evaluation.
Patients were matched against controls for age, parity,
educational level and nationality. We decided on popu-
lation-matching instead of a pair-matching for two
reasons: (i) a pair-matching would have severely limited
the number of patients for evaluation; and (ii) the
aim of matching was to achieve groups with equal or
similar distributions of the matching parameters (and
not to perform a paired analysis). Therefore population-
matching is the better method for this situation. To
compare the role of BMI in the different types of HDP,
we first compared each subgroup of HDP with the same
control group.

Definition criteria of HDP

All diagnoses of HDP were confirmed by medical records
and classified according to the criteria defined by the
ISSHP (International Society for the Study of Hypertension in Pregnancy) [18] as follows: (i) CH, BP \(\geq 140/90\) mmHg before 20 weeks of gestation and after 6 weeks postpartum on two occasions \(\geq 6\) h apart; (ii) GH (gestational hypertension), BP \(\geq 140/90\) mmHg after 20 weeks of gestation and no longer than 6 weeks postpartum on two occasions \(\geq 6\) h apart; (iii) PE, GH/CH + proteinuria \((\geq 0.3\) g/l in a 24-h urine specimen or dipstick proteinuria score \(\geq 1\) in a random urine collection); and (iv) HELLP, haemolysis (lactic dehydrogenase \(\geq 600\) units/l), elevated liver enzymes (aspartate aminotransferase \(\geq 70\) units/l and alanine aminotransferase \(\geq 90\) units/l) and platelet count \(\leq 100\) g/l.

Diagnoses were based on measurements of BP, proteinuria, lactic dehydrogenase, aspartate aminotransferase, alanine aminotransferase and platelet count. To exclude any inconsistencies due to varying hospital criteria, the same diagnostic criteria were applied to all study participants. After reviewing the patients medical records for HDP, 687 pregnancies complicated by GH, PE or HELLP and 601 control pregnancies were included in the study.

**Confounders**

**Age**

Age was defined as age at the delivery of each pregnancy.

**Educational level**

To evaluate educational level, we differentiated between primary school, extended primary school, high school and secondary school.

**BMI**

BMI was calculated as weight per height squared (kg/m\(^2\)). To evaluate BMI at the beginning of pregnancy, maternal weight from 4 weeks before until the end of the 10th week of gestation was used. According to WHO (World Health Organization) criteria [19], women were diagnosed as unweight with a BMI \(\geq 40\) kg/m\(^2\). Height and weight were evaluated from the questionnaire and confirmed by medical records.

The effect of BMI was controlled for age, parity, ethnic background, educational level, smoking status during pregnancy, multiple pregnancies and family risk factors in first- or second-degree relatives (hypertension, heart disease, stroke, diabetes mellitus, increase of blood lipids and HDP).

**Statistical analysis**

Student’s \(t\) test was used to compare group differences in continuous variables. Differences between proportions were analysed using the \(\chi^2\) test. Logistic regression models assessed the association between HDP and BMI after adjusting for confounding variables. We used a forward regression model including only variables that significantly \((P < 0.05)\) influenced risks of GH, PE or HELLP in the univariate analysis. The likelihood ratio test was used to assess first-order interactions with the different risk factors for HDP. All potential confounders listed above were included into the model. Data analysis was performed using the statistical Package of the Social Sciences Advanced Statistics 4.0.

**RESULTS**

Of 687 women in the study group, 78 (11.4%) had GH, 286 (41.6%) PE and 323 (47%) HELLP. Of the 323 pregnancies with HELLP, 179 (55.4%) were complicated by haemolysis in combination with hypertonia and proteinuria.

Table 1 shows the sociodemographic data of patients and controls. Owing to matching, no statistically significant differences for age, parity, educational level and nationality between women developing GH, PE and/or HELLP compared with control women were seen. Marital status was also similar in both groups; however, the study patients worked more often as leading employees, whereas the percentage of working women and trainees was higher in the control group.

Table 2 shows the BMI at the beginning of pregnancy in women developing different types of HDP and the control women. When compared with the controls, women presenting with GH or PE were significantly more overweight or obese at the beginning of their pregnancy. In contrast, BMI at the beginning of the pregnancy showed no association with the development of HELLP. When BMI was investigated as a continuous variable, a statistically significant difference for GH and PE, but not for HELLP, was observed (Table 3).
Distribution of BMI in women with HDP (n = 687)

Statistical evaluation was determined using a \( \chi^2 \) test with the controls as the reference. n.s., Not significant.

<table>
<thead>
<tr>
<th>Type of HDP</th>
<th>GH (n = 78)</th>
<th>PE (n = 286)</th>
<th>HELLP (n = 323)</th>
<th>Control (n = 601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m(^2))</td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>1.0 (0.45–2.24)</td>
<td>1 (0.95–1.04)</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>18.5–24.99</td>
<td>1.0 (1.08–1.11)</td>
<td>1 (1.06–1.15)</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>25–29.99</td>
<td>1.0 (1.06–1.14)</td>
<td>1 (1.05–1.14)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>1.0 (0.96–1.04)</td>
<td>1 (0.95–1.03)</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

| Table 2 | Distribution of BMI in women with HDP (n = 687).

Multivariate logistic regression for predicting the role of pre-pregnancy BMI as a continuous variable in the risk for HDP.

Odds ratios (ORs) refer to each unit increase in BMI. Women with HDP were matched with controls for age, parity, nationality and educational level. Adjusted OR, adjusted for smoking, patients risk factors, multiple pregnancies and family risk factors. n.s., Not significant.

<table>
<thead>
<tr>
<th>Type of HDP</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>1 (1.06–1.18)</td>
<td>1 (1.06–1.17)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PE</td>
<td>1 (1.06–1.14)</td>
<td>1 (1.05–1.14)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HELLP</td>
<td>1 (0.96–1.04)</td>
<td>1 (0.95–1.03)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

| Table 3 | Multivariate logistic regression for predicting the role of pre-pregnancy BMI as a continuous variable in the risk for HDP.

Women with HDP were matched with controls for age, parity, nationality and educational level. Adjusted OR, adjusted for smoking, patients risk factors, multiple pregnancies and family risk factors. For each comparison the normal weight group served as the reference group. Adjusted OR has been calculated for each type of HDP and each weight category taking all potential confounders/risk factors for HDP into account.

<table>
<thead>
<tr>
<th>Type of HDP</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m(^2))</td>
<td>GH (n = 78)</td>
<td>PE (n = 286)</td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>1.0 (1.034–3.665)</td>
<td>1.0 (1.034–3.665)</td>
</tr>
<tr>
<td>25–29.99</td>
<td>1.0 (1.034–3.665)</td>
<td>1.0 (1.034–3.665)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>1.0 (1.034–3.665)</td>
<td>1.0 (1.034–3.665)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI categories (kg/m(^2))</th>
<th>GH (n = 78)</th>
<th>PE (n = 286)</th>
<th>HELLP (n = 323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt; 18.5)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Normal weight (18.5–24.99)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Overweight (25–29.99)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Obesity (≥ 30)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

After controlling for potential confounders, women with a BMI > 25 and < 30 kg/m\(^2\) prior to the 10th week of gestation had a 2-fold risk [95% CI (confidence interval), 1.365–2.983] of developing PE (Table 4). With a BMI ≥ 30 kg/m\(^2\), the risk for developing PE was 3.2-fold (95% CI, 1.7–5.909). Therefore obese women have a higher risk than overweight women of developing PE. The risk for GH was increased by 1.9-fold (95% CI, 1.034–3.665) in overweight women and by 3.8-fold (95% CI, 1.668–9.099) in obese women (Table 4). Neither overweight nor obese women had an increased risk of HELLP (Table 4).

Being underweight at the beginning of pregnancy did not reduce the risk of PE or HELLP.

Smoking during pregnancy [P < 0.005; OR (odd ratio), 0.55] and the presence of family risk factors as defined above (P < 0.0001; OR, 2.0) had an effect independent of BMI on the risk of HDP.

**DISCUSSION**

Recent studies have confirmed the long-suspected association between pre-pregnancy weight and HDP, with estimates of the relative risk ranging from 1.57 to 5.19 [20–22], depending on the definition of overweight and obesity used. Only two reports show opposite outcomes [23,24]. In accordance with other studies [6,12,13,20–30], being overweight and having obesity were significant risk factors for developing PE in our present study. However, our data show that increased BMI at the beginning of pregnancy is a risk factor for GH and PE, but not for HELLP. A comparison of adjusted ORs in different studies is hampered by different BMI categories used to distinguish normal weight from underweight, overweight and obesity, as well as a variety of confounders investigated by multiple logistic regressions. Nevertheless, our adjusted ORs for PE in overweight and obese women are well within the range reported by others [6,12,20,21,23,29]. In contrast, we could not confirm other results that found a reduced risk of developing PE in underweight women [24,26]. However, the number of underweight women in our group was small (n = 47), thus this correlation has to be interpreted with caution.

To our knowledge, only three studies have investigated the role of body weight as a risk factor for developing HELLP: two of these [12,13] investigated HELLP within a category of severe PE; therefore, the differences regarding the role of BMI as a risk factor between different types of HDP could not be analysed separately. The only study differentiating between HELLP and other types of HDP recorded patient weight at admission for delivery [31]. By then BMI will have been influenced by the symptoms of HDP, especially oedema, therefore making it difficult to distinguish between an increased BMI as a cause or a symptom. In addition, weight at admission for delivery varies with gestational age. Furthermore, none of the studies compared the risk of GH, PE and HELLP for the different BMI categories. As reported by Odendal et al. [28] and Moore and Redman [32], the increase in risk caused by augmented pre-pregnancy weight was confined to mild and moderate PE, but was
not present for severe disease. Martin et al. [31] found no significant associations between maternal weight and parameters of HELLP severity. Similar to those results, our present data show that BMI correlates with the risk of GH and PE, but not of HELLP. The difference in the risk profile emphasizes the hypothesis that PE and HELLP develop on the background of variable underlying pathophysiological mechanisms.

Essential hypertension is significantly correlated with weight (P < 0.001), and severe obesity is thought to be associated with PE primarily because of the confounding presence of essential hypertension [31,33]. However, this mechanism is not relevant to HELLP. Elevated BMI might contribute to HDP through other mechanisms. PE develops in two phases, the first of which is characterized by abnormal placentaion with reduced placental blood supply. In the second phase, which is probably caused by oxidative stress, systemic maternal disease occurs [34]. Obesity is associated with dyslipidaemia, such as an increase in plasma/serum triacylglycerols (triglycerides), VLDLs (very-low-density lipoproteins) and small-dense low-density particles, which lead to oxidative stress and to endothelial cell dysfunction, a central pathophysiological feature of PE [22,34,35]. Other mechanisms, such as lipid alterations, which influence the synthesis of the vasoactive components thromboxane and prostacyclins [36], activation of the sympathetic nervous system [37,38], and sleep apnoea, which occurs more often in obese than in normal weight women [39], have also been discussed as risk factors for PE resulting from an increased BMI. Increased cardiac output and oxygen consumption in overweight/obese women may also add to the risk of PE [13]. Apparently, potential mechanisms for transmitting the correlation between BMI and the risk for GH and PE cannot explain why BMI does not act on the risk of HELLP.

Our patients and controls were matched for age, parity, educational level and nationality, so the effect of BMI on the risk of the different HDP is independent of these potential confounders [4,6,31,40]. Since women with diabetes mellitus or gestational diabetes were not included in the patient or control groups, the effect of BMI cannot be explained by an increased number of women suffering from diabetes, a known risk factor for HDP [17]. However, generalization of the results from this study may be limited by its retrospective design.

Despite matching for age and educational level according to high school level, the study patients had significantly more cases in leading employees, whereas in the control group a higher percentage of workers and trainees was found. As an increased BMI is associated with a lower social status [41], this background supports that BMI is a risk factor for PE. Selection bias resulting from the difference in both groups cannot be excluded.

To our knowledge, this is the only study that gives any information on the role of BMI at the beginning of pregnancy in the development of HELLP. It is also the only one to compare the significance of BMI in the development of GH, PE and HELLP. Weight was based on BMI, which is a better overall measure of obesity than weight alone [40], and BMI categories represented normal weight, overweight and obesity according to WHO criteria.

Another strength is the high number of GH, PE and HELLP cases, all of which have been meticulously confirmed by reviewing the medical records of each patient. The ethnic background of our study group is very homogenous and medical records were used to confirm the data. Furthermore, the effect of BMI was controlled for possible confounding factors. As our patients and controls were matched for several factors known for their effect on BMI, the logistic regression model was less complex and therefore more valid.

Although weight reduction might decrease the risk of GH and PE [40,42], such an effect cannot be expected for HELLP according to our results. Research focusing on prophylactic options influencing the risk of HELLP is urgently needed. As a first step to improve clinical management, differences in the risk profile of both diseases might help to understand the underlying pathophysiological mechanisms. Our findings support the hypothesis that PE and HELLP have different underlying pathological mechanisms. Future research will have to ascertain further differences in risk profile, clinical manifestations and therapeutic options of both diseases, which could possibly determine whether HELLP is indeed a severe form of PE or a (partly) independent entity.

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REFERENCES
