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Circulating cardiovascular biomarkers during and after preeclampsia: Crosstalk with placental function?

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in women, yet sex-specific risk factors remain understudied. Preeclampsia and other adverse pregnancy outcomes imply an increased maternal cardiovascular risk. We hypothesized that cardiac troponin T (cTnT), N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) and growth differentiation factor 15 (GDF-15) are increased in such pregnancies and correlate with markers of placental dysfunction. We also investigated these cardiovascular biomarkers 1 or 3 years postpartum.

Prior to delivery, we included serum from 417 pregnant women: 55 early-onset preeclampsia (EO-PE), 63 late-onset preeclampsia (LO-PE), 30 gestational hypertension (GH) and 269 healthy controls. Postpartum, we included 341 women 1 or 3 years after delivery: 26 EO-PE, 107 LO-PE, 61 GH, and 147 healthy pregnancies.

Prior to delivery, median cTnT and NT-proBNP concentrations were higher in women with EO-PE, LO-PE, or GH than in controls. Median GDF-15 was higher in EO-PE and LO-PE compared to controls. Postpartum, GDF-15 was elevated in women with previous EO-PE. Markers of placental dysfunction correlated with CVD biomarkers in pregnancy, but not postpartum.

Our findings underscore the cardiovascular burden of hypertensive disorders of pregnancy and the crosstalk with placental function. The upregulation of circulating GDF-15 following early-onset preeclampsia is in line with the epidemiological excessive risk of premature CVD in this group of women. GDF-15 may be explored for targeting postpartum women with most to gain from intensified preventive follow-up for CVD.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in women, and is responsible for the most years of potential life lost [1]. Meanwhile, cardiovascular research cohorts comprise predominately men [2], although CVD manifests in different ways in men and women [3]. In addition, women are subject to sex-specific cardiovascular risk factors, such as pregnancy-related disorders. For instance, preeclampsia and fetal growth restriction are strongly associated with an increased CVD risk later in life [4]. These pregnancy complications involve various degrees of placental dysfunction. The stressed placenta likely sheds inflammatory and antiangiogenic stress response factors into the maternal circulation, thus promoting endothelial and cardiovascular dysfunction [5]. Pregnancy-related disorders are inadequately taken into account when assessing future cardiovascular risk [5,6]. Further research into surrogate markers of cardiovascular health in women with a history of preeclampsia is thus highly warranted.

Preeclampsia affects 2–8 % of pregnancies worldwide and is an imminent danger to the health of both the mother and the fetus [7]. Early-onset (EO-PE) and late-onset preeclampsia (LO-PE) have partly different etiologies, but both are characterized by excessive placental cellular (syncytiotrophoblast) stress, causing the release of proinflammatory factors to the maternal cardiovascular system [8]. In EO-PE, the placental stress results from poor placentation. LO-PE most often occurs after successful placentation, but excessive syncytiotrophoblast stress may occur secondary to malperfusion in large placentas and in

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ageing/senescent placentas. Placental dysfunction, of whatever cause, results in an altered downstream signaling to the maternal cardiovascular system. Among these proinflammatory substances are anti- and proangiogenic proteins, including antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) that binds and reduces circulating levels of free proangiogeneic placental growth factor (PlGF) [8]. We have proposed that these angiogenic biomarkers are markers of general placental and syncytiotrophoblast (dys)function, not only of preeclampsia itself [8].

Cardiac troponin T (cTnT) is universally used for diagnosing acute myocardial infarction [9]. In the absence of acute or chronic myocardial injury, low levels of cTnT are present in the circulation. Notably, the 99th percentile of the marker is significantly lower in women compared to men, and the prognostic value is higher [10]. Chronic, low-grade elevation of cTnT may identify individuals at high risk of heart failure and cardiovascular death among patients with stable coronary artery disease [11] and in the general population [12]. Cardiac troponins are also elevated in preeclampsia, indicative of myocardial damage during hypertensive disorders of pregnancy (HDP) [13].

The N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) and growth-differentiation factor 15 (GDF-15) are markers of cardiomyocyte stretching [14,15]. NT-proBNP may thus be used to diagnose heart failure [16] and to predict an adverse prognosis in ischemic heart disease [17]. Notably, circulating levels [18] and the prognostic value of NT-proBNP are higher in women than men [19]. In contrast to cTnT and brain natriuretic peptide (BNP), GDF-15 is not exclusively expressed in the heart. In fact, GDF-15 expression in the placenta trophoblasts is higher than in heart tissue [20], although its role in placentation and pregnancy remains unclear. Both NT-proBNP and GDF-15 levels may be upregulated in preeclamptic pregnancies without prepregnancy hypertension or cardiovascular disease [21,22]. Their upregulation prior to preeclampsia development suggest that these biomarkers potentially may help to predict or diagnose preeclampsia either by themselves [23,24] or in concert with sFlt-1/PlGF ratio [24,25].

To gain deeper insights into the different pathologies of HDP, as well as to identify potential distinctions in their biomarker profiles, we measured circulating concentrations of cTnT, NT-proBNP and GDF-15 in women with EO-PE, LO-PE or gestational hypertension (GH) and compared these to healthy controls. Furthermore, we examined the levels of cTnT and NT-proBNP and GDF-15 in relation to clinical and biomarker features of placental (dys)function (i.e., birth weight centiles and maternal circulating sFlt-1 and PlGF). Lastly, we also measured the same cardiovascular biomarkers 1 or 3 years postpartum.

2. Materials and methods

2.1. Study subjects

We analyzed two cohorts from the Oslo Pregnancy Biobank [22]: one from a cross-sectional pregnancy study of women delivering at Oslo University Hospital (OUS), location Ullevål (patients recruited during 2000–2018), and one from the Health After Pregnancy Complications (HAPPY) study in which women (recruited 2014–2018) were followed up 1 and/or 3 years after giving birth at the same hospital [6]. If a woman had been recruited both at 1 and 3 years postpartum, her data and blood samples from her 3-year visit were used in the present study.

The in-patient hospital blood pressure (BP) was based on repeated measurement with a validated device (Dinamap Pro, 100VE, GE Medical Systems Information Technology, Inc. Milwaukee, Wisconsin, USA). At the one-year and three-year postpartum examinations, BP was measured on the right upper arm with an identical BP device to that used prior to delivery, following guidelines from the European Society of Hypertension and European Society of Cardiology [26]. Offspring sex and gestational age specific birth weight percentiles were calculated according to Norwegian ultrasound based percentiles [27].

GH was defined as new onset hypertension (blood pressure $\geq$ 140 mmHg systolic and/or $\geq$90 mmHg diastolic) at $\geq$20 weeks' gestation [28]. Preeclampsia was defined as new onset hypertension and new onset proteinuria at $\geq$20 weeks' gestation [28]. EO-PE and LO-PE were defined as delivery prior to or from 34 weeks' gestation, respectively, in women with preeclampsia [29]. Gestational age at delivery was determined by routine ultrasound at 17–20 weeks' gestation. Women serving as normotensive controls mostly delivered at term and thus were not gestational age matched with women suffering from EO-PE, LO-PE or GH.

Prior to delivery, we included 55 women with EO-PE, 63 with LO-PE, 30 with GH and 269 women with normotensive, euglycemic pregnancies (controls).

From the postpartum cohort we included 341 women, of which 125 were also recruited to our pregnancy cohort. Our postpartum cohort consisted of 26 women who had had EO-PE, 107 LO-PE, 61 GH, and 147 normotensive, euglycemic pregnancies index pregnancies (controls) 1 or 3 years prior. The groups did not differ in median time since index pregnancy at follow-up (data not shown).

For both pregnancy and postpartum cohorts, only women with singleton pregnancies, and no history of hypertension or other inflammatory diseases, were included.

3. Biomarker measurement

As previously described [30], all maternal pregnancy blood samples were drawn predominantly within a week prior to delivery. In our postpartum cohort, fasting blood samples were drawn at follow-up 1 or 3 years after the index pregnancy. Blood samples were stored at −80 °C until analyses.

The maternal PIGF and sFlt-1 serum concentrations from predelivery blood samples were quantified at the Department of Medical Biochemistry, Oslo University Hospital, on a **cobas e** 801 (Roche Diagnostics, Rotkreuz, Switzerland), using the fully automated Elecsys PlGF and sFlt-1 system, according to the manufactureŕs instructions.[‡] Alternatively, the PlGF and sFlt-1 proteins were measured by the same Roche reagents, using an Elecsys 2010 Modular Analytics E170 or a **cobas e** 601 (Roche Diagnostics, Rotkreuz, Switzerland). All concentrations were within the measuring ranges of the PlGF and sFlt-1 assays (3–10,000 pg/mL and 10–85,000 pg/mL, respectively). The coefficients of variation were $\leq$2.1 % for PlGF and $\leq$1.8 % for sFlt-1.

Serum blood samples were thawed from −80° C and analyzed for levels of cTnT, NT-proBNP and GDF-15 at the department for Multidisciplinary Laboratory Medicine and Medical Biochemistry at Akershus University Hospital, using electrochemiluminescence immunoassay Elecsys on the **cobas e** 801 platform (Roche Diagnostics, Rotkreuz, Switzerland). For cTnT and NT-proBNP, routinely analyzed at this laboratory, the measuring ranges are 3–100,000 ng/L and 5–35,000 ng/L, and the analytical coefficients of variation are 3.5 % at 13 ng/L and 2.7 % at 98 ng/L and 3.5 % at 12 ng/L and 2.9 % at 70 ng/L, respectively. GDF-15 was measured according to the manufacturer's instructions and the measuring range is 400–20,000 ng/L. Samples with GDF-15 levels > 20,000 ng/L were diluted 1:20 and reanalyzed. The analytical CV was 0.47 % at concentration 1372–1386 ng/L and 0.61 % at concentration 7373–7458 ng/L.

3.1. Statistical analysis

Continuous variables are presented as medians and interquartile ranges and categorical variables as counts (percent). Comparisons between groups were performed using the non-parametric Mann-Whitney *U* test for continuous variables and the Fisher's exact test for categorical variables. In individuals with biomarker levels below the limit of detection, values were set at the limit of detection (i.e., 3 ng/L for cTnT, 5 ng/L for NT-proBNP and 400 ng/L for GDF-15). The level of

[‡] *COBAS E and ELECSYS are trademarks of Roche.*

significance was set at $p < 0.05$, and we did not correct for multiple testing. Statistical analyses were performed using SPSS version 22.0 (IBM).

4. Results

4.1. Pregnancy phenotypes and placenta-cardiovascular biomarkers

Descriptive statistics as well as biomarker levels during pregnancy are shown in Table 1. As expected, and reported previously by us in part of the same cohort [30], the group of women with EO-PE, LO-PE and GH had higher BMI prior to pregnancy and at delivery, higher systolic and diastolic blood pressure during first 20 weeks of pregnancy, and had an increased antiangiogenic profile (ie. elevated sFlt-1 and/or sFlt-1/PlGF ratio), as compared to controls (Table 1). Also, mean birthweight percentile was lower in the hypertensive groups as compared to controls.

Women with EO-PE, LO-PE and GH had higher median levels of cTnT and NT-proBNP than controls (Table 1). Outside pregnancy, 450 ng/L may be used as a cutoff for circulating NT-proBNP to aid the diagnosis of heart failure in the age-group below 50 years [16]. The women in our study with such high levels all belonged to the preeclampsia groups (EO-PE>; n = 25 and LO-PE; n = 7). Finally, women with EO-PE had significantly lower median levels of GDF-15, whereas women with LO-PE had significantly higher levels as compared to controls (Table 1).

For the total cohort, cTnT and NT-proBNP positively correlated with two proxies for placental dysfunction, namely higher sFlt-1/PlGF ratio (Fig. 1A and 1B) and lower birthweight percentiles (Fig. 2A and 2B). In contrast, GDF-15 did not correlate with sFlt-1/PlGF ratio (Fig. 1C), and correlated positively with birthweight percentiles (Fig. 2C).

Table 1
Pregnancy cohort: clinical pregnancy characteristics and biomarker levels of the 417 recruited women, by index pregnancy outcome groups.

	Control, n = 269	EO-PE, n = 55	LO-PE, n = 63	GH, n = 30
Age at blood sampling (years)	33.8 (30.7 – 36.4)	31.8 (29.9 – 34.4)**	33.4 (29.4 – 35.5)	33.8 (31.1 – 38.2)
BMI before pregnancy (kg/m^2)	22.4 (20.6 – 25.3)	23.7 (21.4 – 26.6)*	22.9 (21.2 – 29.0)	24.6 (22.4 – 28.7)**
BMI at sampling (kg/m^2)	27.7 (25.3 – 31.2)	29.1 (26.1 – 31.9)	29.8 (27.1 – 34.0)***	29.9 (27.5 – 34.0)**
Gestational age at sampling (weeks)	39.0 (38.7 – 39.3)	30.3 (27.6 – 32.7)***	36.9 (34.9 – 37.9)***	38.5 (36.9 – 39.5)*
Gestational age at delivery (weeks)	39.0 (38.7 – 39.3)	30.3 (27.6 – 32.7)***	37.1 (35.3 – 38.1)***	38.5 (37.0 – 39.5)*
Neonatal weight (grams)	3474 (3195 – 3731)	1210 (826 – 1530)***	2610 (2345 – 3248)***	3228 (2831 – 3593)*
Neonatal weight (percentile)	62.4 (34.2 – 82.2)	0.1 (0.0 – 2.3)***	19.6 (4.0 – 53.2)***	44.8 (13.4 – 73.5)*
Newborn sex (girl/boy)	122/147	31/24	31/32	9/21
Primiparous	107 (40 %)	36 (66 %)**	38 (60 %)**	18 (60 %)*
Systolic BP < week 20 (mmHg)	110 (102 – 117)	115 (109 – 126)***	115 (106 – 120)**	122 (120 – 128)***
Diastolic BP < week 20 (mmHg)	68 (62 – 73)	72 (65 – 79) ***	73 (66 – 79) ***	78 (85 – 82) ***
Systolic BP at sampling (mmHg)	120 (114 – 131)	155 (147 – 167)***	154 (146 – 161)***	143 (136 – 154)***
Diastolic BP at sampling (mmHg)	75 (69 – 82)	95 (90 – 105)***	95 (90 – 102) ***	91 (85 – 98) ***
GDM (%)	0 (0 %)	2 (4 %)*	4 (6 %)**	2 (7 %)*
sFlt-1 (pg/mL)	3676 (2747 – 5168)	14,512 (10623 – 21105)***	9753 (8084 – 14962)***	7326 (5371 – 9336)***
PlGF (pg/mL)	171 (110 – 297)	35 (22 – 46) ***	78 (60 – 110) ***	96 (93 – 175)***
sFlt-1/PlGF	22 (10 – 42)	424 (242 – 743)***	135 (95 – 216)***	84 (46 – 123)***
cTnT (ng/L)	3 (3 – 4)	**6 (5 – 10)** ***	**6 (5 – 8)*****	**4 (3 – 6)****
NT-proBNP (ng/L)	29 (19 – 42)	**380 (137 – 860)*****	**155 (73 – 292)*****	**36 (23 – 62)** *
GDF-15 (ng/L)	88,344 (66960 – 117685)	**58,976 (41003 – 96737)*****	**111,835 (74936 – 157403)****	99,051 (70743 – 124303)

Values are given as medians (and interquartile ranges) or numbers (and percentages). Each subgroup was compared to controls using the Mann-Whitney *U* test (continuous variables) and the Fisher's exact test (categorical variables), *p < 0.050, **p < 0.010, ***p < 0.001. EO-PE: early-onset preeclampsia (delivery prior to 34 weeks' gestation), LO-PE: late-onset preeclampsia (delivery from 34 weeks' gestation), GDM: gestational diabetes mellitus, GH: gestational hypertension, BMI: body mass index, BP: blood pressure, cTnT: cardiac troponin T, NT-proBNP: N-terminal pro-Brain Natriuretic Peptide, GDF-15: growth differentiation factor 15.

5. Postpartum phenotypes and cardiovascular biomarkers

Descriptive clinical statistics as well as biomarker levels 1–3 years postpartum are shown in Table 2. As reported previously from a subset of this cohort [6], only the EO-PE group differed significantly in BMI from the control group at postpartum follow-up, whereas all 3 HDP groups had significantly higher systolic and diastolic blood pressures as compared to the control group (Table 2). Postpartum manifest hypertension and prehypertension rates were also significantly higher in all HDP groups compared to controls.

At 1–3 years postpartum, almost all cTnT measurements were at or below the detection limit of the biomarker assay used (3 ng/L; Table 2). Postpartum NT-proBNP levels were similar across all diagnosis groups and no woman had higher values than 235 ng/L. Interestingly, we observed significantly higher postpartum GDF-15 levels in women who had undergone EO-PE compared to healthy controls (Table 2). Neither cTnT, NT-proBNP, nor GDF-15 levels postpartum were associated with index pregnancy birthweight (results not shown).

6. Discussion

In the present study, we add support to our concept of crosstalk between cardiovascular and placental tissues, by demonstrating a correlation between dysregulated CVD biomarkers and clinical proxies of placental dysfunction. These findings are also in line with the concept of a stressed placenta as the culprit in the development of preeclampsia [8]. Although some of our findings are in line with previous studies, notable novelties and differences stand out, especially the associations between cardiovascular biomarkers with placental (dys)function biomarkers.

Cardiac troponin I (cTnI) has previously been found to be elevated in preeclampsia and GH [13]. We expand on these findings by showing increased cTnT in PE, which was evident in both in EO-PE and LO-PE – a distinction that, to our knowledge, has not been made previously. Our findings are expected as higher cardiac troponin levels are associated with hypertension [31] and systemic inflammation [32] – two hallmarks of preeclampsia [8]. The observation that cTnT was elevated in GH compared to controls, but to a lesser extent than in EO-PE and LO-PE, fits well with HDP representing a continuum along an increasing severity of cardiovascular and placental disease.

The main stimulus for secretion of NT-proBNP is the stretching of cardiac myocytes [14]. Accordingly, women with preeclampsia present with elevated levels of NT-proBNP [23]. We show that women with EO-PE as well as women with LO-PE had higher levels of NT-proBNP than controls. Surprisingly, in the present study, women with GH stand out among women with HDP as they have almost comparable low NT-

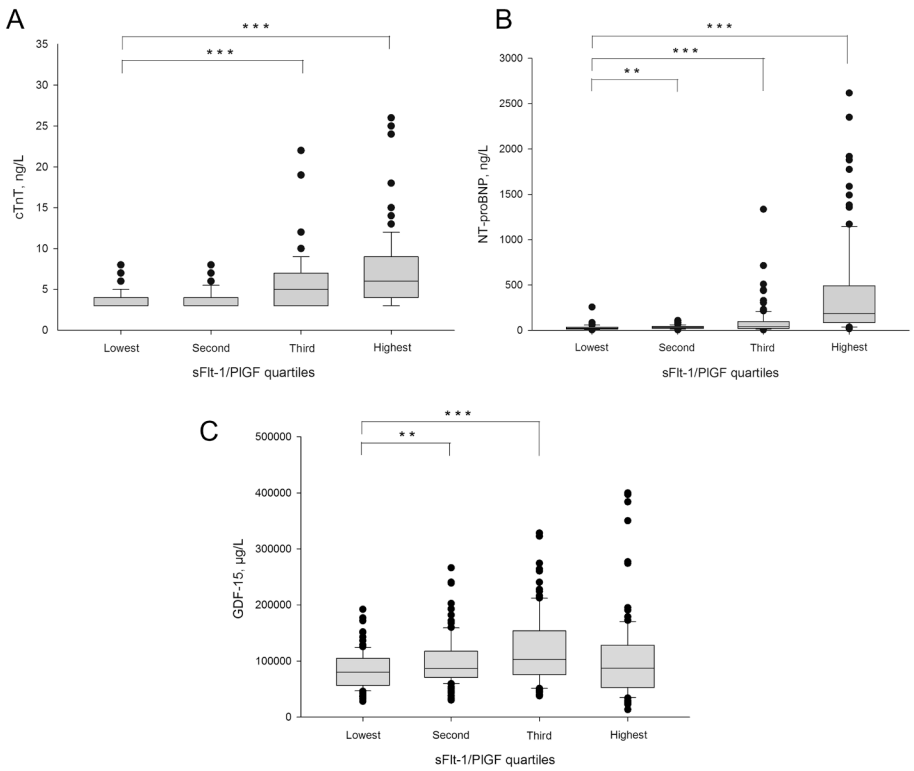

Fig. 1. Pregnancy cohort (N = 417 women): Boxplots of circulating A) cardiac troponin T (cTnT), B) N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) and C) growth differentiation factor 15 (GDF-15) levels, all in ng/L. The total pregnancy study cohort was categorized into sFlt-1/PlGF ratio quartiles. Biomarker concentrations are shown in boxplots as 10th percentile (lower whisker), 25th percentile, median (horizontal box line), 75th percentile, 90th percentile (upper whisker), as well as outliers. The second, third and highest sFlt-1/PlGF quartiles were compared to the lowest quartile using the Mann-Whitney *U* test, *p < 0.050, **p < 0.010, ***p < 0.001.

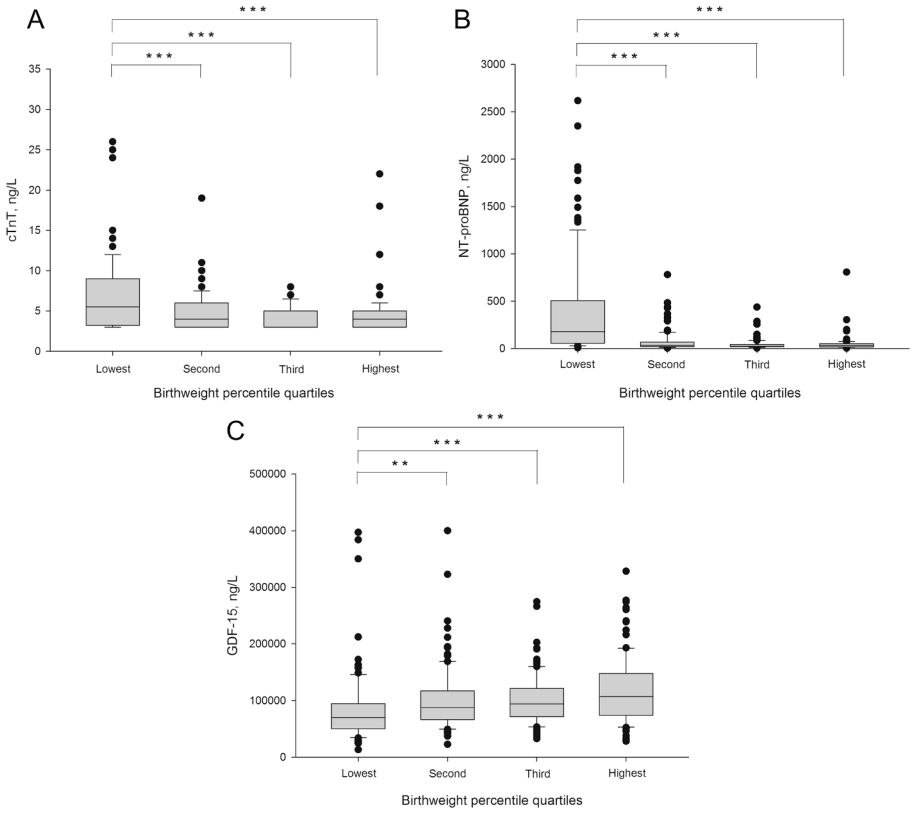

Fig. 2. Pregnancy cohort (N = 417 women): Boxplots of circulating A) cardiac troponin T (cTnT), B) N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) and C) growth differentiation factor 15 (GDF-15) levels, all in ng/L. The total pregnancy study cohort was categorized into birthweight percentile quartiles. Biomarker concentrations are shown in boxplots as 10th percentile (lower whisker), 25th percentile, median (horizontal box line), 75th percentile, 90th percentile (upper whisker), as well as outliers. The second, third and highest birthweight percentile quartiles were compared to the lowest quartile using the Mann-Whitney *U* test, *p < 0.050, **p < 0.010, ***p < 0.001.

proBNP levels to controls. This observation is somewhat in conflict with a previous publication reporting substantially increased levels of NT-proBNP in women with GH [23]. Both studies use the same diagnostic criteria, the same reagents and have comparable numbers of participants. Notably, NT-proBNP correlates with left ventricular mass index in women with preeclampsia [33]. Therefore, we cannot rule out that the slightly discrepant findings regarding NT-proBNP in GH may be due to more women with clinically severe GH and a more affected left

Table 2
Postpartum cohort: clinical characteristics and biomarkers 1 or 3 years postpartum of the 341 recruited women, by index pregnancy outcome groups.

	Control, n = 147	EO-PE, n = 26	LO-PE, n = 107	GH, n = 61
Age at blood sampling (years)	34.6 (31.8 – 37.5)	36.2 (32.4 – 38.0)	34.8 (32.2 – 38.2)	34.9 (33.1 – 38.1)
BMI at sampling (kg/m^2)	22.9 (20.5 – 26.0)	26.0 (22.2 – 29.7)*	23.7 (21.5 – 26.2)	24.4 (21.2 – 27.4)
Gestational age at delivery (weeks)	39.0 (38.6 – 39.7)	30.7 (29.3 – 33.0)***	38.0 (37.0 – 39.4)***	39.3 (37.9 – 40.4)
Neonatal weight (grams)	3320 (2750 – 3650)	1265 (987 – 1537)***	2857 (2465 – 3486)**	3355 (2756 – 3672)
Neonatal weight (percentile)	45 (7 – 72)	0 (0 – 6)***	26 (4 – 63)*	39 (8–72)
Newborn sex (girl/boy)	77/70	13/13	52/55	29/32
Primiparous (yes %)	72 (49 %)	18 (69 %)*	84 (78 %)***	36 (59 %)
Systolic BP (mmHg)	108 (102 – 114)	116 (105 – 123)**	113 (107 – 120)***	120 (111 – 128)***
Diastolic BP (mmHg)	63 (59 – 58)	72 (67 – 77)***	70 (63 – 74)***	74 (67 – 80)***
Hypertension[a]	0 (0 %)	1 (4 %)	5 (5 %)*	4 (7 %)**
Prehypertension[b]	12 (8 %)	8 (31 %)**	22 (21 %)**	28 (46 %)***
GDM (%)	0 (0 %)	1 (4 %)	10 (9 %)***	4 (7 %)***
cTnT (ng/L)	3 (3 – 3)	3 (3 – 3)	3 (3 – 3)	3 (3 – 3)
NT-proBNP (ng/L)	44 (31 – 67)	58 (27 – 88)	48 (31 – 66)	53 (30 – 72)
GDF-15 (ng/L)	409 (400 – 506)	**492 (400 – 566)***	428 (400 – 542)	440 (400 – 506)

Values are given as medians (and interquartile ranges) or numbers (and percentages). Each subgroup was compared to controls using the Mann-Whitney *U* test (continuous variables) and the Fisher's exact test (categorical variables), *p < 0.050, **p < 0.010, ***p < 0.001. EO-PE: early-onset preeclampsia (delivery prior to 34 weeks' gestation), LO-PE: late-onset preeclampsia (delivery from 34 weeks' gestation), GDM: gestational diabetes mellitus, GH: gestational hypertension, BMI: body mass index, BP: blood pressure, DM: diabetes mellitus (type 1 /type 2). [a] Hypertension: Blood pressure ≥ 140 mmHg systolic and/or ≥90 mmHg diastolic. [b] Prehypertension: Blood pressure 120–139 mmHg systolic and/or 80–89 mmHg diastolic, cTnT: cardiac troponin T, NT-proBNP: N-terminal fragment of the B-type natriuretic peptide prohormone, GDF-15: growth differentiation factor 15.

ventricle in the study by Sedlecki et al [23] as compared to ours.

While GDF-15 expression is scarce in most tissues, this peptide hormone is abundantly expressed by the placenta trophoblasts [20]. This is reflected in our results, where circulating GDF-15 is orders of magnitude higher during pregnancy than postpartum. In other tissues, GDF-15 expression may be induced by various stresses, such as inflammatory signalling molecules [34] and hypoxia [35]. The same stimuli presumably affect GDF-15 expression in the placenta. Accordingly, in a partly overlapping cohort (86 subjects in common: 24 EOPE21 LOPE, 4 GH and 37 controls) with the one included in the present study, we have previously observed increased levels of GDF-15 in women with preeclampsia who delivered after gestational week 36 [22]. Several studies have since investigated GDF-15 in preeclampsia, with conflicting results. Chen and colleagues reported reduced GDF-15 levels in both EO-PE and LO-PE compared to gestational age-matched controls [36]. Conversely, two later studies showed increased levels in EO-PE and LO-PE [24,37], and one study reported higher levels of GDF-15 in EO-PE [38]. These discrepancies may be due to differing population characteristics and methods. Here, in our extended cohort, we repeat our previous findings of increased GDF-15 in LO-PE. In accordance with Chen et al., we also observe lower levels of GDF-15 in women with EO-PE. However, because GDF-15 increases throughout pregnancy [36], and we lack gestational age-matched controls for our EO-PE group, we are unable to conclude if this difference is due to pathophysiological differences, or simply reflects the gestational changes of pregnancy. Lastly, median GDF-15 level in GH was similar to the control group, indicating a less severely affected cardiovascular system in GH than in the two preeclampsia subgroups. This finding, together with less dysregulated placenta biomarker levels and more normal baby weight percentiles in GH than in EO-PE and LO-PE, is in line with our concepts of a gradually increased cardiovascular and placental dysfunction phenotype within the heterogeneous HDP group, with GH pregnancies situated in the "milder" area of disease spectrum.

We have proposed that the severity of HDP manifestation depends on the maternal response to syncytiotrophoblast stress and placental dysfunction [8]. In line with this argument, we here demonstrate a clear association between two proxies for placental dysfunction – a high sFlt-1/PlGF ratio, and low birthweight percentile – and the cardiovascular stress markers cTnT and NT-proBNP. The same association was not observed between placental dysfunction and GDF-15. However, as the main source of GDF-15 during pregnancy is the placenta, this observation may be confounded by our lack of gestational age-matched controls for the EO-PE group, which simultaneously presented with the highest median sFLt-1/PlGF ratio, the lowest median birthweight percentile and the lowest median GDF-15 ratio.

A recent study showed no difference in GDF-15 levels between small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) neonates at birth [39], but found at 4 month's age an apparent reduction in GDF-15 in the SGA group compared to AGA. The authors propose that these lower levels in smaller infants could be adaptive, to promote catch-up in weight. In support of this proposal, GDF-15 has previously been implicated as a regulator of energy homeostasis [40]. Whether our study's association between birthweight percentiles and GDF-15 is related to energy homeostasis remains to be investigated, as GDF-15 is related to a variety of disease processes.

A recent study showed no increase in circulating cTnI approximately 9–10 years postpartum following EO-PE [41]. Median cTnI levels in cases and controls were 2.50 ng/L and 2.35 ng/L respectively. In accordance with this study, we were unable to detect any group differences in cTnT values postpartum. However, as almost all measurements were at or below our limit of detection, limited conclusions can be drawn based on these data. Neither were we able to detect any effect of previous HDP on NT-proBNP level postpartum. In controls, we detected higher NT-proBNP levels postpartum than during pregnancy, which is in line with a previous publication [21].

The normalization of cTnT and NTproBNP in the postpartum period among women with previous HDP may be surprising, considered the epidemiologically well documented increased CVD risk in these women. Based on our observations, these biomarkers accurately reflect the acute cardiac stress of hypertension during pregnancy, but may be unsuited for the early identification of non-pregnant and otherwise healthy premenopausal women at high risk of premature CVD. Studies including a higher rate of women with well-known high risk factors for CVD, such as obesity, may possibly conclude otherwise, but such high risk women are likely to be identified with traditional cardiovascular risk score systems without the use of blood-based CV biomarkers. Long-term studies with hard endpoints are required to draw definitive conclusion regarding the cardiovascular predictive properties of cTnT and NTproBNP levels during pregnancy or postpartum.

To our knowledge, the only study investigating GDF-15 levels in women following HDP is our previous small study of 22 women 5–8 years after preeclampsia [42]. In the present larger study, we found that women with previous EO-PE had significantly higher GDF-15 values compared to women who had undergone a healthy pregnancy 1–3 years prior. This is worrisome, as circulating GDF-15 is a predictor of all-cause mortality [43]. Moreover, GDF-15 did not correlate with BMI postpartum (results not shown). Thus, we speculate that the observed increased GDF-15 levels in women with previous EO-PE reflect a state of prolonged low-grade systemic inflammation. This assumption is in line with our recent report of an excessively activated immune system

postpartum in this EO-PE group, with elevated levels of the immune modulator soluble HLA-G [30].

Approximately half of the women with previous preterm pre-eclampsia (delivery prior to gestational week 37) show persistent left ventricular dysfunction one year postpartum [44]. On average, these women have higher left ventricular wall stress index and altered left ventricular geometry compared to women with previous term pre-eclampsia or healthy pregnancies [44]. Such structural remodelling is likely due to an excessive accumulation of collagen within the myocardium, due to prolonged biomechanical stress [45]. As mentioned, NT-proBNP and GDF-15 are upregulated by mechanical stretching of cardiomyocytes [14,15]. The presently observed elevated GDF-15 levels might thus reflect altered cardiac remodelling in women with EO-PE 1 or 3 years prior. Accordingly, NT-proBNP levels were also elevated in women with previous EO-PE compared to controls, although this difference did not reach statistical significance.

Our findings underscore the cardiovascular short- and long-term burden of preeclampsia. The observed dysregulated biomarker profiles are often associated with cardiomyocyte damage, ventricular chamber wall stress, systemic inflammation and hypoxia. The postpartum upregulation of GDF-15 in women who underwent EO-PE is in line with large-population-based studies showing that these women are at particularly high risk of CVD and premature death [4]. Our study provides increased insight into how pregnancy and placental dysfunction associate with maternal cardiovascular risk factors.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Roche Diagnostics donated biomarker reagents in-kind (sFlt-1, PlGF, cTnT, NT-proBNP and GDF-15). Anne Cathrine Staff has received recompensation from Roche Diagnostics for Advisory board service in 2018 regarding preeclampsia screening. Roche Diagnostics had no further involvement in study planning, collection or interpretation of data, writing of the manuscript, or the decision to submit the article for publication.

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