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Peripartum dynamics of ischemia and heart failure biomarkers: the impact of delivery mode

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ABSTRACT

Background: The uterus and its myometrium undergo several changes during delivery. In labor, the myometrium performs contractions to expel the newborn. In a cesarean section, however, the myometrium is incised. Little is known about labor-induced changes in biomarkers that are known to rise during injuries and exhaustion of another muscle, the heart. These markers can also be produced by the myometrium, especially damaged myometrium. Since labor is known to cause slight myocardial challenge, physiological changes in cardiac biomarkers in the context of labor versus after an incision of the uterus are of new interest. Here, we question whether cardiac biomarkers could also be produced by the uterus. If this were the case, the interpretation of the myocardial ischemic marker peripartum needed a revision. This study investigated whether cardiac biomarkers might be influenced by uterine activity or injuries from cesarean sections.

Methods: We conducted a prospective study on the peripartum trajectories of creatine kinase (CK, cardiac isoenzyme CK-MB), high-sensitivity cardiac troponin-T (hs-cTnt), and N-terminal pro-B-type natriuretic peptide (NT-Pro-BNP) in 44 cardiologically healthy pregnant women. The participants were stratified by delivery mode: cesarean section (CS, $n=24$) versus vaginal delivery (VD, $n=20$).

Results: Our findings indicate that ischemia biomarkers (hs-cTnT, CK and CK-MB) increase more during the postpartum period than they do after a cesarean section, whereas NT-Pro-BNP levels increase after cesarean section. These elevations remained within normal ranges and were not associated with clinical symptoms.

Conclusion: Biomarker levels differ based on delivery mode, indicating that mode of birth influences biomarker fluctuations postpartum within a physiological range. The incision of the uterus does not reveal higher marker levels than contractions do; therefore, this kind of myometrial damage is not associated with an increase in ischemic biomarkers. The observed elevations are linked to slight myocardial damage in the peripartum phase after labor, comparable to exercise. The myometrium does not appear to provide evidence for a clinically meaningful contribution based on peripheral measurements of highly sensitive troponin, CK and CKMB.

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Cardiac biomarkers; peripartum myocardial stress; vaginal delivery; cesarean section; maternal cardiovascular adaptation; postpartum recovery

Introduction

Throughout the human life span, the uterus displays a striking capacity for regeneration. The endometrium/myometrium undergoes extensive remodeling and cellular changes before, during, and after pregnancy [1,2].

Different modes of delivery of a child reflect various physiological challenges to the mother. Labor contractions are painful, regular, and present with a change in cervical dilation and/or effacement [3]. In contrast, cesarean delivery is a surgical procedure that involves delivering a baby through an abdominal incision (laparotomy) and a uterine incision (hysterotomy) [4]. Pregnancy and delivery could lead to increases in both muscular and cardiac biomarkers. For example, several reports indicate elevated activity of serum CK and its isoenzyme CKMB in maternal blood during childbirth. The

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uterus and placenta, two organs that are reported to embody substantial amounts of these enzymes and that actively participate in the process of labor, are thought to release these enzymes into the circulation during labor [5].

At the cardiological site, pregnancy and labor are known to be challenges. Particularly in the peripartum period, there is a physiologically high hemodynamic load on the heart. During the first trimester, there is an increase in the serum levels of progesterone and relaxin, peptide hormones produced by the corpus luteum and placenta, which promote systemic vasodilation, leading to a progressive decrease in systemic vascular resistance (SVR). The SVR decreases by 35 to 40% during pregnancy and returns to prepregnancy levels two weeks postpartum [6]. Consequently, systemic blood pressure decreases by 5–10 mmHg during pregnancy, with diastolic blood pressure decreasing more than systolic blood pressure. Systemic blood pressure begins to rise in the third trimester and returns to prepregnancy values 6–12 weeks postpartum [6]. In accordance, heart rate increases linearly during pregnancy by 10 to 20 beats per minute over baseline and returns to preconception values six weeks postpartum [7]. In the peripartum phase, the circulating blood volume increases immediately postpartum due to uterine contraction and an increase in preload due to unloading of the inferior vena cava, which leads to an increase in stroke volume as well as an increase in cardiac output of 60–80%. This value quickly returns to prepregnancy levels within 1 to 2 h after delivery and to prepregnancy levels within two weeks after delivery [8,9]. In addition to these acute hemodynamic changes, ventricular remodeling occurs during pregnancy, with an increase in left ventricular wall thickness of 28% to 52% over prepregnancy values. Some recent studies also reported an increase in right ventricular volume and mass of 40% during pregnancy. The physiological hypertrophy of the ventricular system returns to the prepregnancy state four weeks postpartum [10,11]. This reflects blood pressure normalization, whereas other parameters, such as heart rate, recover earlier postpartum.

Ultimately, pregnancy and delivery, whether through vaginal delivery or cesarean section, impose significant stress on the maternal body. Physical and psychological efforts could result in cardiac stress, potentially reflected by an increase in the levels of myocardial ischemia and heart failure markers.

To understand more about muscular and cardiac biomarker dynamics in different delivery modes and their associated maternal distress, as well as myometrial damage, we conducted this prospective study. Here, we aim to describe the peripartum courses of creatine kinase and its cardiac isoenzyme CK-MB, high-sensitivity cardiac troponin-T and NT-Pro-BNP and compare these two groups (Group I: Cesarean section "CS", Group II: vaginal delivery "VD").

Methods

To address this question, we conducted a prospective cohort study from May 2023 to January 2024 at the St. Hedwig University Hospital of Gynecology and Obstetrics, Regensburg, Germany.

A total of 44 consecutively presenting pregnant women were included in this study. Data were collected *via* "Viewpoint 6.0" (GE Healthcare) and "SAP Healthcare." Medical history, pregnancy characteristics, delivery mode, neonatal data and delivery records were retrieved from "Viewpoint 6.0" and anonymized.

The inclusion criteria were as follows: Group 1 (cesarean section) consisted of pregnant patients with an indication for elective cesarean section, without uterine contractions, with no current or past cardiovascular events or symptoms and who provided written consent for study participation.

Group 2 (vaginal delivery) included pregnant women with no current or past cardiovascular events or symptoms, with no previous operations on the uterus and written consent for study participation.

Women with an indication for secondary (intrapartum) cesarean section or pregnant women with cardiovascular diseases were excluded.

For all included patients, a detailed medical history focused on cardiovascular risk factors, which varied between low and moderate risk for cardiovascular disease (CVD). The following criteria were considered cardiovascular risk factors (CVRFs): arterial hypertension or gestational hypertension; substance abuse: nicotine/alcohol; obesity (body mass index > 30 kg/m^2); hyperlipidemia or

dyslipidemia; diabetes mellitus and positive family history. Fetal growth restriction (FGR); premature placental abruption and preterm birth were also as pregnancy-related risk factors considered.

An electrocardiogram was performed using CARDIOVIT AT-10 plus prepartum as a baseline and to detect any preexisting pathologies. A second ECG was conducted within the first 24 h postpartum to identify any new pathologies. Patients were also questioned about cardiac symptoms, such as dyspnea, chest pain, and palpitations, during or after delivery.

Laboratory tests were conducted at the Institute of Laboratory Medicine, Microbiology and Infection Prevention, Hospital of the Order of St. John, Regensburg, Germany, with samples taken at three points: prepartum, 24 h postpartum, and 48 h postpartum. All blood samples were sent to the laboratory within one hour and immediately centrifuged and analyzed. The following parameters were measured on an integrated Cobas PRO analyzer (Roche, Mannheim, Germany): creatine kinase (CK) (ClinChem)); limit of detection "LoD" 7 U/L); creatine kinase MB (CKMB) (Elecsys); LoD 3 U/L, or 0.3 ng/ml; limit of blank "LoB" 0.1 ng/ml; and limit of quantification "LoQ" 1 ng/ml). High-sensitivity troponin T (Elecsys TNT hs; LoD 3 ng/L, LoB 2.5 ng/L and LoQ 13 ng/L) and NT-pro-BNP (Elecsys proBNP II, LoD 5 pg/mL, LoB 3 pg/mL and LoQ 50 pg/mL) were analyzed according to the manufacturer's instructions.

The following factors were examined: age at delivery, prepregnancy BMI (in kg/m^2), gestational age at delivery in days (measured by the first day of last menstruation or by early vaginal ultrasound between the 9th and 12th weeks using the crown–rump length of the embryo), birth weight of the child, child length, birth percentile according to Voigt, child sex and the pH value of the umbilical cord artery.

Statistical analysis was performed *via* GraphPad Prism 10 software. Data distribution was assessed for normality using the Shapiro–Wilk test. As the majority of variables did not follow a normal distribution, non-parametric statistical methods were used for analysis. To compare two independent groups, the Mann–Whitney U test was used. To compare multiple related dependent groups (three groups) to control for the temporal progression of a parameter, the Friedman test and Dunn′s multiple comparison test were employed. Correlation analysis was conducted *via* Spearman's rank correlation. This investigation was designed as an exploratory analysis; therefore, no formal sample size calculation was included in the study protocol.

Due to the limited sample size and the resulting risk of model overfitting, we refrained from performing linear mixed-effects modeling, as such models require larger datasets to provide stable and reliable estimates.

Both measures, median (IQR) and mean ± SD are presented to allow comparison with prior literature and to provide a comprehensive description of data distribution.

The graphs were created *via* GraphPad Prism 10.

A p-value greater than 0.05 was considered the threshold for significance.

Results

The total cohort of 44 women was stratified by delivery mode into women with cesarean section (CS, $n = 24$) and women with vaginal delivery (VD, $n = 20$).

All study participants were nonsmokers, had no arterial hypertension, no diabetes, and no positive family history of cardiovascular diseases and initially presented no pathologies in either the ECG or the biomarkers measured prepartum.

The median age of the overall cohort was 32.0 years, with an interquartile range (IQR) of 28.0–36.7 years, with no significant difference between the two groups ($p = 0.07$).

The median gestational age for the entire cohort was 273 (IQR 273–280) days. A significant difference between the two groups was observed, with participants in Group 1 (CS) having a slightly lower median gestational age of 273 (IQR 266–280) days than those in Group 2 (VD), which had a median gestational age of 287 (IQR 280–294) days ($p < 0.0001$). The strict inclusion criteria of CS without any labor onset results consecutively in a lower gestational age at term birth.

The median birth weight with an interquartile range for the entire cohort was 3291 g, with an IQR of 3109–3682 g. The median birth weight in Group 1 (CS) was significantly lower ($p = 0.04$) than that

in Group 2 (VD), with a median birth weight of 3232 g and an IQR of (2958–393 g) for Group 1, whereas the median birth weight in Group 2 was 3417 g, with an IQR of (3230–3935 g).

In this study, birth percentiles were calculated *via* the Voigt method.

Further characteristics of the obstetrical and neonatal outcomes are shown in Table 1. The results of the measured cardiac biomarkers are shown in Table 2.

During the postpartum phase, cardiovascularly healthy women exhibit a significant increase in cardiac troponin-t levels following delivery (overall cohort), peaking within the first 24 h postpartum to 6.0 (5.0–8.0) ng/L, $p < 0.0001$ vs. prepartum), (Figure 1(a)) and declining within 48 h to 5.5 (4.2–7.0) ng/L, $p < 0.01$ vs. prepartum, $p < 0.05$ vs. 24 h after delivery (Figure 1(a)). These values remained within the normal range (<14 ng/L).

In accordance, compared with those at prepartum, CK and CK/MB levels (entire cohort) were significantly elevated at 24 h postpartum ($p < 0.0001$, Figure 1(b and c)), and these levels remained elevated at 48 h postpartum (p value "ns" vs. 24 h postpartum and p value < 0.0001 vs. prepartum) (Figure 1(b and c)).

Importantly, these elevations in hs-cTnt, CK and CKMB were significantly greater in women who underwent vaginal delivery (group 2) than in those who underwent cesarean section (group 1) (see Figure 2(a–c)). There was a statistically significant difference between the two groups at 24 h and 48 h postpartum.

Table 1. Baseline characteristics.

	Overall cohort $N = 44$		Group 1 (CS) $N = 24$		Group 2 (VD) $N = 20$		
Parameter	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	*p*-value
Maternal age (year)	32.0 (28.0–36.7)	32.3 ± 6.0	34.0 (30.0–37.0)	33.9 ± 5.5	30.0 (26.0–35.0)	30.6 ± 6.2	0.07
BMI (kg/m^2)	24.2 (21.7–29.3)	25.5 ± 5.1	23.7 (21.0–28.5)	24.8 ± 5.1	25.1 (21.9–31.0)	26.2 ± 5.1	0.54
Gestational age (days)	273 (273–280)	279 ± 10	273 (266–280)	270 ± 5	287 (280–294)	287 ± 7	<0.0001
Birth weight (g)	3291 (3109–3682)	3392 ± 510	3232 (2958–3393)	3254 ± 538	3417 (3230–3935)	3544.3 ± 442.5	0.04
Birth length (cm)	51.0 (50.0–53.0)	51.4 ± 2.5	51.0 (49.0–52.0)	50.6 ± 2.2	51.0 (51.0–54.7)	52.3 ± 2.7	0.03
Arterial umbilical cord-pH	7.3 (7.2–7.3)	7.3 (7.2–7.3)	7.3 (7.2–7.3)	7.3 (7.2–7.3)	7.2 (7.1–7.2)	7.2 ± 0.09	0.03
Birth percentile (%)	35.0 (18.0–65.2)	35.0 (18.0–65.2)	36.5 (25.5–66.0)	36.5 (25.5–66.0)	24.0 (14.2–61.7)	36.7 ± 29.7	0.27

Table 2. Peripheral controls of the measured parameters.

	Overall cohort $N = 44$		Group 1 (CS) $N = 24$		Group 2 (VD) $N = 20$		
Controls of the measured parameters	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	*p*-value
hs-cTnt 1 (ng/L)	5.0 (4.0–6.0)	5.1 ± 1.7	5.0 (4.0–6.0)	4.9 ± 1.5	5.0 (4.0–6.0)	5.3 ± 2.0	0.60 (ns)
CK 1 (U/L)	55.0 (37.2–87.0)	72.2 ± 63.4	45.0 (27.0–62.0)	64.8 ± 75.0	60.0 (47.0–108.0)	80.2 ± 48.3	0.01 (*)
CK MB 1 (U/L)	0.0 (0.0-0.0)	1.7 ± 5.4	0.0 (0.0-0.0)	1.8 ± 6.3	0.0 (0.0-0.0)	1.6 ± 4.3	0.99 (ns)
NT-Pro-BNP 1 (pg/ml)	30.5 (16.5–68.0)	48.9 ± 47.6	28.0 (11.0–68.0)	45.9 ± 57.8	50.0 (24.0–73.5)	52.2 ± 34.2	0.13 (ns)
hs-cTnt 2 (ng/L)	6.0 (5.0–8.0)	6.8 ± 2.5	6.0 (4.2–7.0)	5.8 ± 1.3	7.0 (6.0–11.0)	8.0 ± 3.0	0.01 (*)
CK 2 (U/L)	154.5 (105.2–261.7)	238.9 ± 296.3	111.0 (102.0–147.0)	136.9 ± 74.6	226.0 (197.0–403.0)	355.1 ± 396.2	< 0.001 (***)
CK MB 2 (U/L)	0.0 (0.0–30.2)	25.0 ± 56.1	0.0 (0.0-0.0)	19.2 ± 76.5	22.0 (19.2–48.6)	32.0 ± 26.1	< 0.001 (***)
NT-Pro-BNP 2 (pg/ml)	51.5 (27.7–85.5)	87.7 ± 112.1	48.5 (27.7–84.2)	69.5 ± 74.3	61.0 (22.0–86.0)	108.6 ± 143.1	0.59 (ns)
hs-cTnt 3 (ng/L)	5.5 (4.2–7.0)	6.1 ± 2.3	5.0 (4.0–6.0)	5.1 ± 1.4	7.0 (5.0–8.0)	7.1 ± 2.7	0.01 (*)
CK 3 (U/L)	149.5 (119.0–222.2)	193.2 ± 151.2	136.0 (102.7–168.7)	152.2 ± 93.3	192.0 (146.0–305.0)	244.2 ± 187.3	0.02 (*)
CK MB 3 (U/L)	0.0 (0.0–22.9)	12.3 ± 16.8	0.0 (0.0–5.5)	7.1 ± 14.8	18.0 (0.0–26.8)	18.5 ± 17.5	0.04 (*)
NT-Pro-BNP 3 (pg/ml)	83.0 (47.2–160.7)	132.0 ± 147.0	129.0 (45.7–222.5)	149.4 ± 117.4	64.0 (38.0–107.0)	116.4 ± 178.6	0.02 (*)

(ns): not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ Control 1: prepartum, Control 2: 24 h postpartum and Control 3: 48 h postpartum.

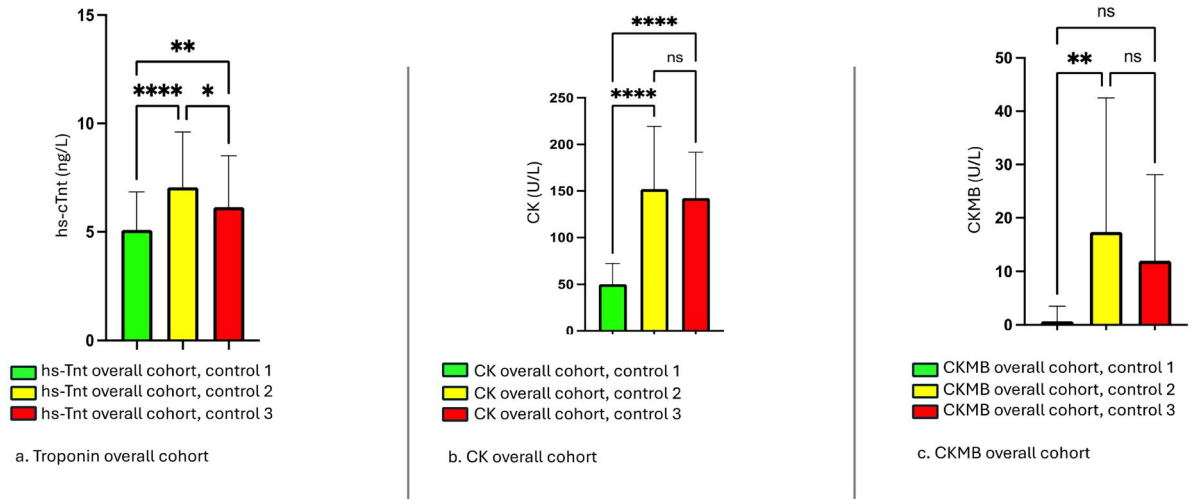

Figure 1. The overall cohort: controls at three time points. (ns): not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Control 1: prepartum; Control 2: 24 h postpartum; Control 3: 48 h postpartum.

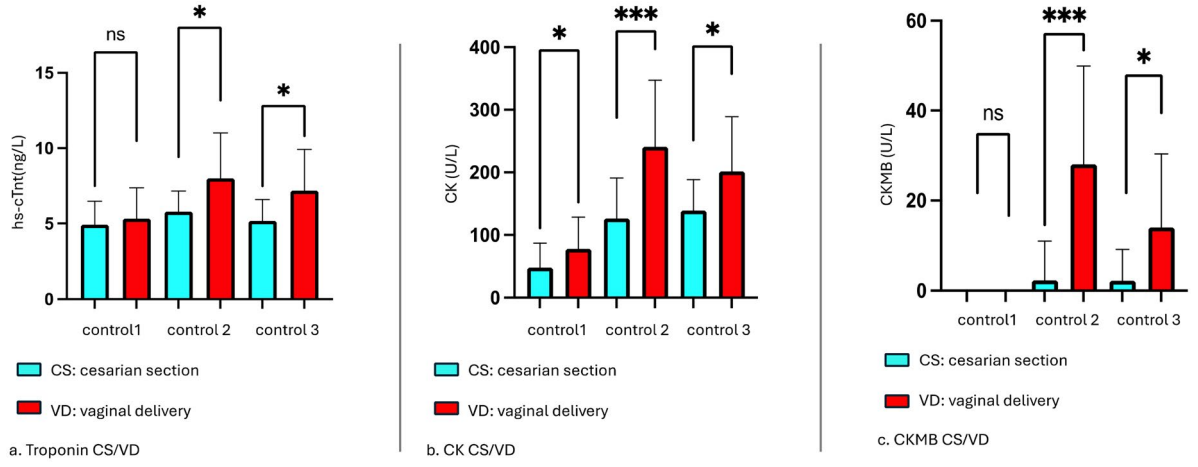

Figure 2. Controls at three time points between Group 1 (CS) and Group 2 (VD). (ns): not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Control 1: prepartum; Control 2: 24 h postpartum; Control 3: 48 h postpartum.

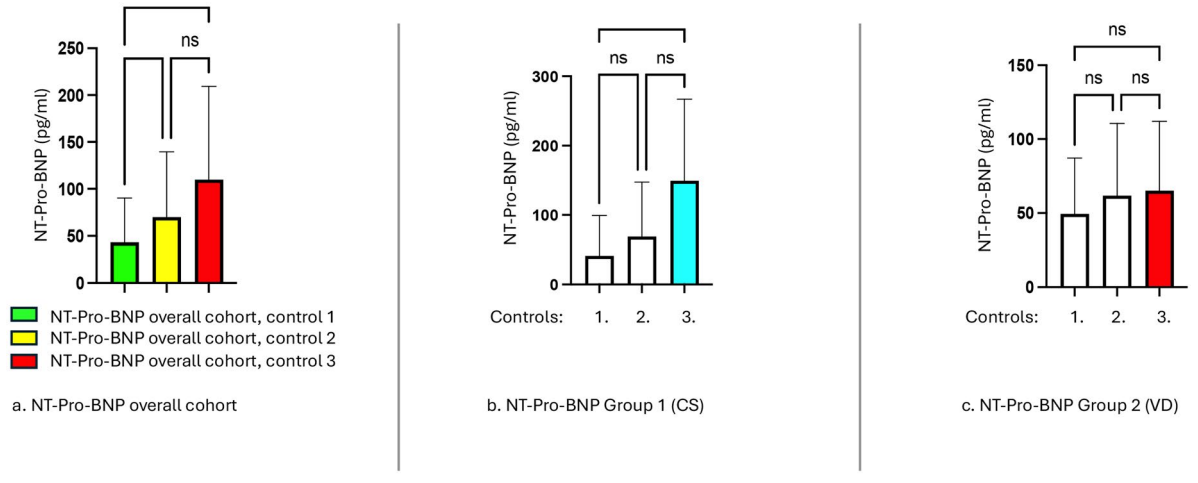

Figure 3. NT-Pro-BNP overall cohort, Group 1 (CS), and Group 2 (VD), controls at three time points. (ns): not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Control 1: prepartum; Control 2: 24 h postpartum; Control 3: 48 h postpartum.

A significant elevation in NT-Pro-BNP levels was also observed postpartum (at 24 h, $p < 0.05$ vs. prepartum), with further elevation at 48 h postpartum ($p < 0.001$ vs. prepartum) (see Figure 3(a)).

However, in contrast to troponin, CK and CKMB, a significant increase in NT-Pro-BNP was observed only in women who underwent cesarean section and was significant only at 48 h postpartum (control 3) ($p < 0.0001$) (see Figure 3(b and c)).

Discussion

This study evaluated the course of several cardiac ischemic markers in the peripartum phase. Additionally, the levels in women with uterine contractions and without uterine contractions but with a cesarean section were analyzed and compared. The purpose of this study was to determine whether uterine contractions and/or damage to the uterine muscle by hysterotomy in the context of cesarean sections may influence the levels of cardiac ischemic markers. The purpose of this study was based on the hypothesis that the myometrium could also produce the named substances, which are comparable to those in the myocardium. If this is the case, the interpretation of cardiac ischemic markers used for cardiac diagnosis needs revision in the peripartum phase regarding the delivery mode. Additionally, this study was conducted in healthy cardiac women without any pregnancy complications and without any complications during labor or cesarean section.

In summary, only physiological changes in the examined parameters were observed. In conclusion, neither myometrial exhaustion nor myometrial incisions reveals a relevant increase in cardiac ischemic marker levels. Therefore, the interpretation of elevated biomarkers is analogous to that of nonpregnant women and is irrespective of myometrial damage.

However, distinct fluctuations were observable between labor and elective CS. These fluctuations and their potential impacts are discussed below.

- Troponin-T:

  In our study, we observed a significant increase in troponin-T levels during the postpartum phase among cardiovascularly healthy parturients, with the peak occurring within the first 24 hours postdelivery. These values were above the LoD of hs-cTnt (3 ng/L) but remained within the normal range (<14 ng/L). ECG monitoring postpartum and the medical history taken after delivery, particularly concerning cardiac symptoms, did not indicate any clinical relevance of this increase. Studies by Shivvers et al. (1999) and Furenäs et al. (2020) provided context: Shivvers et al. reported that troponin-I levels increased postdelivery, suggesting minor myocardial cell damage, whereas Furenäs et al. reported elevated hs-cTnt during peripartum periods but below ischemia thresholds, affirming current diagnostic criteria [12,13].

  Our study yielded comparable results regarding hs-cTnt across the cohort, confirming the aforementioned statement independently of delivery mode, i.e. labor activity. Furthermore, we analyzed the difference between the two groups classified by mode of delivery. Our aim was to identify the potential effects of delivery mode on cardiac stress, which remains subclinical. This observation revealed a significant difference between the two groups, with troponin-T levels in control 2 (24 h postpartum) and control 3 (48 h postpartum) being significantly greater in group 2.

  Several factors contribute to this result, primarily labor pain accompanied by the release of catecholamines into the peripheral blood, resulting in tachycardia, and an increase in the myocardial contractile force leads to membrane damage and a subsequent increase in the membrane permeability of cardiomyocytes. This ultimately results in the release of cytosolic troponin, which normally accounts for approximately 3–8% of the total cardiac troponin-T within myocardial cells, into the peripheral circulation [14]. Several questions arise in this context, with the most significant being whether this increase in hs-cT does not influence the actual prognosis or subsequent cardiovascular outcomes. Additionally, whether vaginal delivery causes more cardiac stress than cesarean delivery without labor is unclear. It should

be emphasized that troponin elevation in this context does not necessarily reflect myocardial necrosis but may represent reversible membrane leakage or physiological cardiomyocyte stress.

The fact that markers for cardiac ischemia also exhibit a physiological increase due to various daily activities, such as any type of exercise or situations involving increased anxiety, contradicts this hypothesis. During the subsequent follow-up (control 3, 48 h postpartum), these values decreased, which was consistent with the pattern of hs-cTnt after physical activity. This was demonstrated in a 2019 study conducted in the United Kingdom by Baker et al. who examined the kinetics of cTnt after physical activities. Their review of cTnt kinetics revealed a pattern of increase and peak within the first 4 h postexercise, followed by a decline within 24 h. In contrast, myocardial necrosis exhibits a later cTnt peak with a slower decline over several days [15]. Since values in all participants in our study remained below the upper limit thresholds and the study participants did not develop symptoms of cardiovascular origin, this elevation can be considered physiological or even interpreted as beneficial cardiac training. To assess the long-term effects on the prognosis of these women, particularly regarding cardiac events, further follow-up and careful monitoring are needed.

- CK and CK-MB
  In a 1996 study of 50 women with normal pregnancies and uncomplicated vaginal deliveries, researchers reported a significant increase in CK levels during labor, reaching 2–4 times the baseline values 24 hours postdelivery and then gradually returning to baseline. Nulliparous women had higher CK levels than multiparous women did. The MB isoenzyme, a cardiac-specific component, contributed significantly to the CK increase. There was a correlation between the duration of active labor and the total and MB-CK activities. None of the participants showed clinical or electrocardiographic signs of myocardial damage [16]. This result was revealed in another study by Chemnitz et al., who reported that CK and its isoenzyme CK-MB are influenced by muscle and uterine muscle activity [17]. Our study revealed similar results, with a statistically significant increase in CK and CK-MB levels during labor and the postpartum phase, peaking within the first 24 hours after delivery (control 2) and declining over the next 24 hours (control 3). A novel aspect of our study was that we compared two groups on the basis of the mode of delivery used to determine its impact. We found a significant increase in CK levels in the vaginal labor group (Group 2) but not in the cesarean section group (Group 1). CK-MB is not cardiac-specific and is also present in the uterus and placenta, accounting for approximately 8–20% of the total CK. Therefore, determining the exact origin of CK-MB elevation, whether cardiac or from the uterus or placenta, remains challenging [18]. Therefore, several factors, such as labor duration and birth percentiles, which are associated with increased uterine muscle activity, could contribute to CK and CK-MB release into the peripheral blood. Further observations in our study revealed a significant positive correlation between newborn weight and CK and CK-MB levels in control 3. We conclude that increasing birth weight is associated with more uterine activity to deliver the baby accompied by an enhancedphysiological biomarker release rather than evidence of myocardial necrosis.
- NT-Pro-BNP

Biomarkers such as brain natriuretic peptide (BNP) and its metabolite NT-Pro-BNP are used to diagnose heart failure outside of pregnancy [13,19]. In general, BNP remains stable during normal pregnancy [20,21]. A 2022 review by Esbrand et al. revealed that normal NT-Pro-BNP levels correlate with healthy pregnancies, whereas elevated levels are associated with adverse outcomes [22]. Burlingame et al. (2017) reported increases in BNP and NT-Pro-BNP in the first 48 h postpartum, returning to nonpregnant levels within 6–12 weeks [19]. Our study confirmed this finding, showing a significant NT-Pro-BNP increase within 24–48 h postpartum, below the normal upper limit for heart failure diagnosis. Our study compared peripartum NT-Pro-BNP levels between two groups (cesarean section and vaginal labor). We found a significant increase in NT-Pro-BNP 24–48 h postpartum in the cesarean section group but not in the vaginal labor group.

Since NT-proBNP has a half-life of 90–120 min [23], it is possible that we did not capture its peak increase in the vaginal delivery group during the first measurement. In contrast, NT-proBNP may be released later in the cesarean section group.

Potential hypotheses for this delayed release include, first, slower uterine involution following cesarean section, leading to delayed autotransfusion and subsequent cardiac volume load. Second, delayed oxytocin release is observed after cesarean section compared with vaginal delivery, which, owing to the antidiuretic effect of oxytocin, may contribute to increased volume load [24]. These mechanisms are speculative and should be considered as hypotheses rather than proven explanations.

Furthermore, NT-proBNP could serve as a potential marker reflecting hemodynamic changes in postpartum women, particularly after cesarean section.

If we consider NT-proBNP as a predictive parameter for prognosis and outcomes in the peripartum phase, the question arises whether cesarean section itself constitutes a potential risk factor for cardiac stress during this period.

Although all participants had an uneventful clinical course, subclinical cardiac damage cannot be entirely ruled out. Further prospective studies with echocardiographic correlation and strain analysis at various postpartum intervals would be valuable to clarify the prognostic significance.

Despite these valuable findings, our study has several limitations, including its small sample size. As one limitation, we did not include a group of patients with intrapartum CS, which means a CS following uterine contractions over a distinct time. Further research is needed to confirm these findings and understand cardiovascular changes during and after pregnancy. Biomarkers alone may not fully capture subclinical cardiac changes, so imaging techniques such as echocardiography and long-term follow-up studies are recommended for a deeper understanding.

This study has several limitations that should be considered when interpreting the findings. The relatively small sample size limits statistical power and generalizability. No formal sample size calculation or power analysis was performed prior to the study; therefore, the findings should be interpreted as exploratory and hypothesis-generating, and the study may be underpowered to detect smaller effects. In addition, significant baseline differences between groups, particularly in gestational age and birth weight, represent theoretically confounders that may have influenced biomarker levels. Gestational age and birth weight were earlier/lower in cases with a planned CS compared to spontaneous labor onset. However, since the results were within the physiological range near term, it is unplausible that the primary results are altered to a relevant extent. As no multivariable adjustment or mixed-effects modeling was performed, residual confounding cannot be excluded.

Although the study includes repeated measurements within individuals and comparisons between groups over time, more advanced statistical approaches such as linear mixed-effects models (including time × delivery mode interaction) were not applied, which limits the ability to fully assess differential biomarker trajectories. Furthermore, several relevant obstetrical variables that may affect biomarker release—such as duration of labor, parity, use of analgesia or anesthesia, induction or augmentation of labor, duration of the second stage of labor, and intrapartum fluid administration—were not systematically analyzed, restricting adjustment for additional confounders.

The exclusion of intrapartum (secondary) cesarean sections further limits the interpretation, as it precludes differentiation between the effects of uterine contractions and surgical intervention. Moreover, the study is based solely on peripheral biomarker measurements without complementary cardiac imaging or functional assessment, so conclusions regarding myocardial stress remain indirect. Finally, proposed mechanistic explanations should be interpreted as speculative, as they were not directly investigated in this study. This limitation restricts the ability to disentangle the contributions of uterine contractions and surgical incision of the myometrium to biomarker release.

Overall, our findings suggest that peripartum biomarker elevations are physiological and influenced by delivery mode, with greater increases after vaginal delivery reflecting transient myocardial stress rather than clinically relevant injury. These findings are important for the interpretation of cardiac biomarkers in postpartum women and highlight the need for further studies, including imaging and larger cohorts.

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Ethics approval and consent to participate

The study was approved by the Ethics Committee of the University of Regensburg (Approval Number: [21-2427-101]). All participants provided written informed consent prior to participation. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Author contributions

CRediT: **I. Abou Tabikh**: Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Writing – original draft; **N. Mawas**: Methodology, Project administration; **M. Kappelmeyer**: Formal analysis; **S Wagner**: Project administration; **L. S. Maier**: Project administration; **A. Köninger**: Project administration.

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No potential conflict of interest was reported by the author(s).

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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