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Severe Fetal Distress and Placental Damage Might Be Associated with High Troponin I (cTnI) Levels in Mothers

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 40
Final Diagnosis: cTnI elevation of unknown etiology
Symptoms: Epigastric pain
Medication: —
Clinical Procedure: —
Specialty: Obstetrics and Gynecology

Objective: Unknown ethiology
Background: Troponin I is the gold standard for the diagnosis of adult acute coronary syndrome. Although it is known that a hypoxic fetus may produce cTnI, fetal cTnI passage in maternal blood has never been documented.
Case Report: We report a case where the rise of cTnI in the blood of a pregnant woman was not related to maternal heart disease. Instead, it might be suggestive of a fetal cardiac origin, as there was a severe placental insufficiency with a fetal intrauterine growth restriction.
Conclusions: This study suggests that the rise of cTnI in maternal blood in a cardiovascular healthy pregnant woman might have a fetal origin. After having excluded any maternal causes, cTnI elevation could be explained with the transfer of fetal cTnI through an injured placenta.

MeSH Keywords: Fetal Growth Retardation • Fetal Hypoxia • Placenta Diseases • Troponin I

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Background

Troponin is a protein complex located in the thin filaments of the sarcomere in all striated muscles, including skeletal and heart, and it is involved in the regulation of muscle contraction. This complex is composed of three protein subunits: troponin C (TnC) which binds calcium, troponin T (TnT) which binds tropomyosin, and troponin I (TnI) which is an inhibitory subunit. TnI acts by blocking action-myosin interactions and thereby mediating striated muscle relaxation [1]. The measurement of cardiac-troponin I (cTnI) is the gold standard for the diagnosis of adult acute coronary syndrome (ACS) and indicates the presence of myocardial injury [2,3]. We report a case of a pregnant patient with an altered blood cTnI level of unknown etiology, not apparently affected by any type of maternal cardiac or non-cardiac disorders. In contrast, the maternal cTnI level increase might be suggestive of a fetal cTnI origin in a complex scenario of severe fetal hypoxia, fetal myocardial tissue massive necrosis area, and severe placental damage.

Case Report

A primigravida 40-year old Caucasian female was diagnosed at 19 gestational weeks with a severe early intrauterine growth restriction (IUGR). Ultrasound biometry showed a harmonic fetus with the estimated fetal weight below the fifth percentile associated with an anhydramnios. Moreover, there was a pathologic feto-placental Doppler Flowmetry: reversal of umbilical artery end-diastolic flow (REDF), brain sparing, and high flow resistance in both uterine arteries were recorded. The parents of the fetus had normal anthropometric parameters: the mother was 167 cm tall and weighed 58 kg; the father was 165 cm tall and weighed 91 kg. During the nuchal translucency (NT) ultrasound at 12 weeks and three days of amenorrhea the crown rump length (CRL) was 58 mm according to the last period reported by the women. The previous medical history of the patient was negative, and she was not under any medications. The analysis of chorionic villi previously performed at 11 gestational weeks, demonstrating a 46XY normal fetal karyotype. Furthermore, at 16 weeks of pregnancy, the ultrasound biometry performed by her gynecologist was in accord to amenorrhea and the amniotic fluid volume was normal (Figure 1) During the second trimester, the patient developed IUGR and a borderline blood pressure level (130–140/85–90 mm Hg).

After the diagnosis of severe IUGR, we discussed with the patient the benefits and risks of both induced abortion and progression of the pregnancy, including intrauterine fetal death and development of severe hypertension and pre-eclampsia. In accordance with the Italian law, the patient decided to interrupt the pregnancy, and therefore she was admitted to our inpatient service.

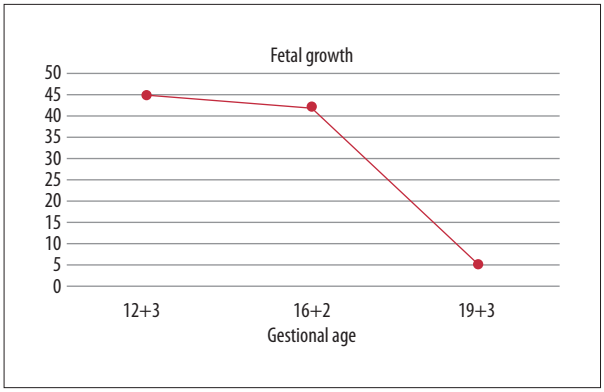

Figure 1. Diagram of fetal percentile ultrasound measurements in serial examinations.

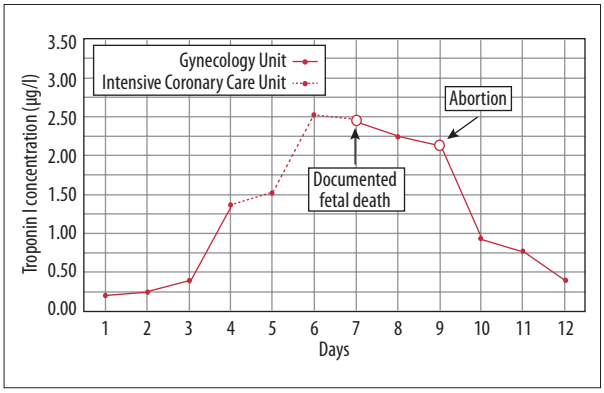

Figure 2. Troponin I time lapse: Evaluation of Troponin I concentration (µg/L) in maternal blood during the period of patient admission (days).

Blood pressure was measured twice a day and resulted below 140/90 mmHg; therefore, no treatment for pregnancy hypertension was adopted. Serological tests for pre-eclampsia were performed (proteinuria, platelet count, and liver-function test) with negative results. Surprisingly, during the second day of hospitalization, the patient developed a persistent epigastric pain, without headache or scotomas; according to our clinical practice, electrocardiogram (ECG) and blood cardiac markers evaluation were performed. The ECG was negative, while the cTnI level showed a concentration above the normal range (0.21 µg/L; normal values 0.00–0.09 µg/L) and its amount increased steadily in the following measurements (Figure 2). The maternal echocardiography showed no structural abnormalities, with an ejection fraction of 65%. According to cardiologist, before starting the induction of legal abortion by target drug delivery by prostaglandins treatment, the patient was admitted to the intensive coronary care unit (ICCU) to evaluate if any type of cardiac or non-cardiac disorders could justify the high level of cTnI.

A progressive increase of cTnI values (1.53–2.53 µg/L) was recorded during the ICCU admission. Nevertheless, no ECG

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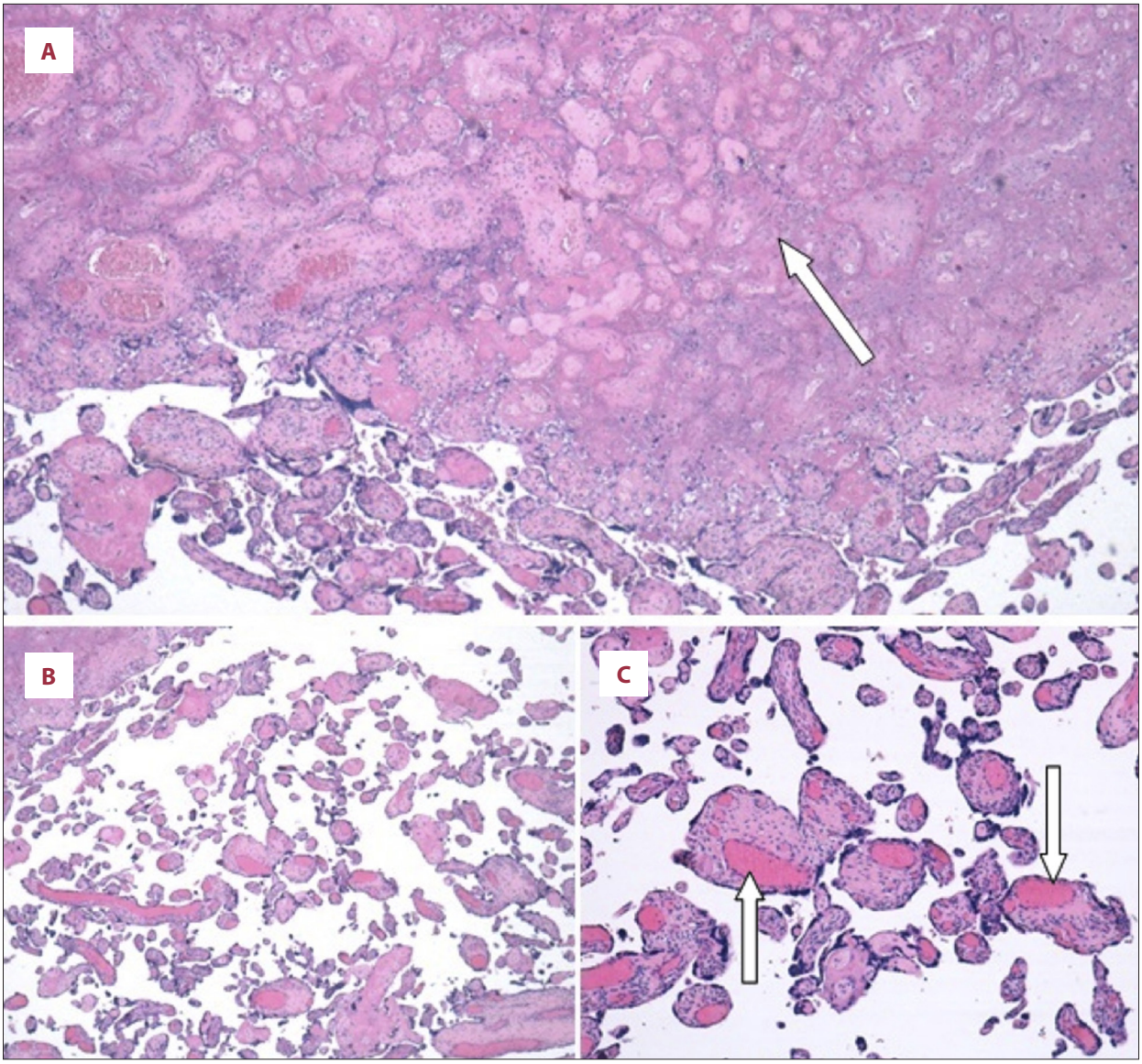

Figure 3. Microscopic examination of placenta. (**A**) Placental infarcts: widespread ischemic necrosis of placental villi (arrow) (hematoxylin–eosin staining, ×4). (**B**) Hypermature villi related to gestational age (hematoxylin–eosin staining, ×4). (**C**) High-power field magnification showing villous vessels with marginal and vascular ectasia (arrows) (hematoxylin–eosin staining, ×10).

alterations continued to be observed and the performed computed tomography coronary angiography (CTCA) showed normal patterns. Overall, no signs of ischemia, pericarditis or myocarditis events were detected. Besides, the presence of symptoms related to other diseases causing TnI increase were evaluated, but no diseases, such as acute pulmonary embolism or end stage renal disease, were detected. Therefore, the patient was sent back to our obstetric unit for termination of pregnancy.

At the patient's re-admission to the obstetric unit, the diagnosis of spontaneous fetal demise was performed by ultrasound. Immediately, after the intrauterine fetal death, cTnI levels were evaluated, and its concentration started to decrease. In order to induce the delivery, a treatment with gemeprost (1 mg vaginal treatment, each three hours) was started. After five doses, the patient delivered. The fetus was analyzed macroscopically, and was found to be normal, whereas the placenta showed multi-infarcts in the chorionic plate (>80% of the size). The fetal autopsy did not show macroscopic damaged of the heart but the histopathological investigation underlined the presence of a "massive necrosis area" in the fetal myocardial tissue. Therefore, the fetus had a myocardial infarction. The microscopic examination of the placenta confirmed the presence of multi-placental-infarcts (Figure 3A), and, at high-power field

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(HPF) magnification, hypermature chorionic villi (Figure 3B) with vascular ectasia were observed (Figure 3C). Therefore, diagnosis of severe damage of the placenta was made. After the termination of the pregnancy, cTnI values continued to decrease steeply. A negative ECG was documented every day during hospitalization and the patient was discharged after three postoperative days.

Discussion

In this reported case, we highlight three aspects: 1) cTnI levels increasing in the blood of an apparently healthy pregnant woman, 2) fetal cTnI production, and 3) fetal cTnI transplacental passage.

First, concerning the increase of cTnI in the blood of an apparently healthy pregnant woman, there are scanty and controversial data in the literature exclusively related to pre-eclampsia/eclampsia patients [4,5]. Regarding this topic, Fleming et al. demonstrated that gestational hypertension is associated with an increase of cTnI concentration due to myofibrillary damage caused by hypertension. In these women, median cTnI values were 0.118 ng/mL and 0.155 ng/mL, in women affected by gestational hypertension and proteinuric hypertension, respectively; these values were significantly different and about five higher compared to the median value (0.03 ng/mL) of non-affected women [4]. However, other authors [5] did not register any cTnI increase in pre-eclampsia/eclampsia patients. Similar controversial results were reported by Pergialiotis et al. in a recent review [6]. Concerning the data reported in this manuscript, our patient's cTnI levels were much higher than both pathological and normal levels reported by Fleming et al. (50–80 times and 10–20 times, respectively). Additionally, we observed a steep rise before delivery. Furthermore, the patient underwent several investigations and she did not show either clinical or laboratory signs of pre-eclampsia or other diseases related to cTnI increase (pericarditis, myocarditis, pulmonary embolism, and kidney disease).

As a consequence of the observations carried out from this case report, we wonder whether fetal cTnI may contribute to increases of maternal cTnI in blood.

Second, concerning fetal cTnI production, in the literature there were some preliminary studies. Cardiac myocytes express two different types of TnI isoform: the skeletal slow twitch TnI isoform and the adult cardiac TnI isoform (cTnI). The skeletal slow twitch TnI isoform is produced during fetal life and first weeks of life, while cTnI is expressed from the first days after birth to adulthood [7]. Hypoxic/asphyxia stress may trigger the expression of cTnI before birth [8]. Several clinical studies confirmed this hypothesis [8–11]. In particular, Clark et al. measured cTnT levels in umbilical cord blood at the delivery showing that troponin levels are significantly higher in newborns with respiratory distress with respect to healthy newborns (mean values: 0.031 ng/mL versus 0.010 ng/mL respectively, $p<0.001$). Moreover, troponin is indicated by Clark et al. as independent predictor of developing respiratory distress in a multiple logistic regression (r=0.20, $p<0.0003$) [9]. Trevisanuto et al. [10] and Tűrker et al. [11] obtained similar results. Furthermore, Trevisanuto et al. [8] compared umbilical cord blood cTnI values of 19 distressed newborns to mother TnI. They reported that in newborns the cTnI median value was 0.24 µg/L, while blood cTnI in mothers was negative (0.04 µg/L) suggesting that the cTnI was produced exclusively by the fetus [8]. In our case report, we assert that the fetus, prior to death, suffered from a severe hypoxia producing acute myocardial infarction and because of that cTnI might have been produced in high quantities, though the fetal weight was low.

Finally, concerning the fetal cTnI passage in maternal blood, it is generally accepted that cTnI does not cross the placenta. Indeed, the molecular weight of cTnI (24 kD) is above the average weight of the molecules that usually cross the placental barrier; furthermore, an experimental study on mice demonstrated that troponin cannot be transferred through the normal placenta [12]. In our patient, we believe that the severely injured placenta might have allowed the passage of fetal cTnI into the maternal blood. In support of our hypothesis, the levels of cTnI started to decrease with fetal death and normalized after pregnancy termination.

Conclusions

In conclusion, we report an interesting case of elevated cTnI in a pregnant woman without documented cardiac disease or other non-cardiac disease related to TnI increase. Our observed clinical and pathological findings lead us to suggest that severe fetal hypoxia could stimulate and induce an earlier fetal cTnI production and that injures affecting placenta could allow the moving of fetal troponin into the maternal blood. Further studies need to confirm our preliminary hypothesis. In addition, our report suggests that during pregnancy in cardiovascular healthy women, if a cTnI level increase is diagnosed, the co-existence of fetal hypoxia and placental injury should be considered and investigated.

Conflict of interests

None.

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