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PATHOMORPHOLOGICAL FEATURES OF MYOCARDIAL MICROCIRCULATION IN PERIPARTUM CARDIOMYOPATHY ACCORDING TO PREGNANCY PARITY

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ABSTRACT

Peripartum cardiomyopathy (PPCM) is a form of heart failure that appears near the end of pregnancy or in the months following delivery. Although the clinical picture is dominated by reduced left ventricular function, changes in the small vessels that supply the myocardium may be an important part of the disease. Pregnancy-related antiangiogenic signals and hormonal changes may reduce capillary stability, while inflammatory and fibrotic reactions affect surrounding cardiac tissue. The possible influence of pregnancy parity on these changes is still unclear. Objective. To examine published morphological and experimental evidence of myocardial microcirculatory injury in PPCM and assess what can currently be concluded about its association with first and subsequent deliveries. Materials and methods. A descriptive comparative review of five publications concerning myocardial capillary ultrastructure, angiogenic imbalance, prolactin-related endothelial injury, and reproductive history was undertaken. Histological findings were considered separately from experimental mechanisms and population-based associations. Results. The reviewed literature describes endothelial remodeling, capillary lumen abnormalities, disturbed angiogenic signaling, and interstitial tissue changes. Experimental studies support roles for reduced angiogenic

protection, increased sFLT1 activity, and a 16-kDa prolactin fragment. Clinical data suggest a relationship between parity and PPCM risk but do not provide reliable parity-specific measurements of myocardial capillary damage.

Relevance of the research problem

Peripartum cardiomyopathy remains an important problem because it affects women during a period when the circulatory system is already adapting to major physiological demands. Pregnancy increases circulating blood volume and cardiac workload. In most women these changes are tolerated, but in PPCM the myocardium develops systolic dysfunction that cannot be fully explained by ordinary pregnancy adaptation. Clinical symptoms may resemble common complaints of late pregnancy, making early recognition difficult. For pathologists, the central question is why a heart that was previously able to meet circulatory needs begins to fail during this relatively short period.

For many years attention was directed mainly toward the contractile cells of the heart, myocardial enlargement, inflammation and interstitial fibrosis. More recent work has suggested that the coronary microvascular network also deserves careful examination. Capillaries provide oxygen and nutrients to individual cardiomyocytes and are essential for normal energy metabolism. Even when larger coronary arteries are not obstructed, changes in small-vessel endothelial cells or in capillary density may reduce effective tissue perfusion. This makes endothelial morphology and angiogenic regulation relevant to understanding PPCM.

The relationship between microcirculation and pregnancy is especially important because the placenta produces factors that can influence the maternal vasculature. Patten and colleagues showed that an imbalance between proangiogenic and antiangiogenic signals can contribute to cardiac dysfunction in experimental systems and in women with PPCM. Their findings particularly implicated soluble fms-like tyrosine kinase-1, which antagonizes vascular growth factor activity. Elevated antiangiogenic signals in late pregnancy may expose vulnerable myocardium to additional vascular stress [4].

Another proposed mechanism involves prolactin. Research by Hilfiker-Kleiner and colleagues demonstrated that cleavage of prolactin produces a biologically active fragment with antiangiogenic and proapoptotic properties. Experimental exposure to this fragment damaged the myocardial capillary network. This work offers a possible connection between hormonal change after childbirth and microvascular pathology, although animal findings cannot be interpreted as identical to every human case [5].

An additional unanswered question concerns parity, meaning the number of previous deliveries. The risk of PPCM may be influenced by reproductive history, maternal age, hypertensive disorders, and other conditions. However, parity should not be confused with

multiple gestation: a woman giving birth to twins is experiencing one delivery, even though placental and circulatory demands may differ from a singleton pregnancy. A reported epidemiological association between parity and PPCM does not, by itself, establish that capillary damage is more severe after repeated deliveries [1, 2].

For these reasons, a focused pathological review is needed. It should describe what has actually been observed in cardiac microvessels, separate experimental mechanisms from human histology, and identify which measurements would be required to compare women with first and subsequent pregnancies. This distinction is especially important when preparing a scientific article from previously published evidence rather than presenting new biopsy material.

Aim of the study

To analyze the morphological changes of myocardial microcirculation reported in peripartum cardiomyopathy and to assess the possible relationship between these changes and pregnancy parity using published histopathological, experimental and clinical evidence.

Materials and methods

This article was prepared as a narrative literature-based comparative analysis. The primary material consisted of five scientific publications listed in the original thesis. The reports covered the clinical association of parity with PPCM, ultrastructural examination of myocardial capillaries, experimental angiogenic regulation and prolactin-associated vascular injury. The articles were considered according to their design and the type of evidence they provided. No new patients were recruited, no myocardial tissue was sampled for this article, and no original laboratory measurements or patient-level statistical tests were performed. For the pathological component of the comparison, attention was paid to endothelial cell shape and continuity, capillary lumen configuration, signs of endothelial apoptosis or obstruction, alterations of the surrounding interstitium, and the possible relation of microvascular injury to cardiomyocyte damage. In experimental investigations, the review focused on the balance between factors that support vessel maintenance and factors that inhibit angiogenesis. Clinical investigations were assessed for information on reproductive history, rather than treated as direct microscopic studies. The evidence was organized into three related levels: direct observations in myocardial tissue; experimental mechanisms that may explain microvascular injury; and clinical associations between reproductive characteristics and PPCM. This organization was used to avoid combining unrelated populations or presenting animal-derived observations as human biopsy findings. Numerical information is retained only when reported in the source literature. A summary table is provided for transparent comparison. Three locations are reserved for histological or ultrastructural microphotographs from the cited publications, pending confirmation of image reuse permissions.

Results and discussion

The comparative review showed that alterations of the myocardial microvascular bed form a meaningful component of the pathology described in peripartum cardiomyopathy. The principal

findings across the examined publications included endothelial injury, remodeling of capillary walls, irregularity or narrowing of vascular lumina, impaired vascular maintenance, and changes in the neighboring interstitial tissue. These abnormalities did not constitute one uniform lesion. Rather, different studies described different parts of a complex process that may include vascular stress, altered signaling and secondary myocardial remodeling.

Myocardial capillaries are small enough that their structural alterations may be difficult to assess using routine histology alone. An ordinary haematoxylin and eosin section may show the position of vessels in the myocardium, the presence of inflammatory cells and the relation of vascular profiles to muscle fibers. Ultrastructural examination can provide a closer view of endothelial cytoplasm, junctional regions and the capillary lumen. These complementary methods are useful because functional vascular impairment may occur before an obvious change in the overall number of vessels becomes apparent.

Fidziańska and colleagues provided direct ultrastructural evidence of remodeling of myocardial capillaries in PPCM. Their report described endothelial changes, luminal obstruction and apoptosis-associated abnormalities, with additional alterations in the myocardial interstitium. The importance of this observation is that it places microvascular injury within the cardiac tissue itself, rather than inferring it only from blood tests or clinical signs. The reported findings support a possible link between damage to the endothelial lining and insufficient myocardial perfusion. They do not, however, establish a separate morphological pattern according to parity.

Changes in endothelial structure may have several consequences. Swelling or disruption of the endothelium can disturb local exchange between blood and tissue. Capillary obstruction may reduce the number of channels actively carrying blood. When tissue perfusion becomes insufficient, cardiomyocytes may experience metabolic stress, and the interstitium can undergo remodeling. Fibrosis developing near injured vessels can further separate capillaries from muscle cells. These processes should be described carefully: the coexistence of fibrosis and capillary damage does not prove that one always precedes the other.

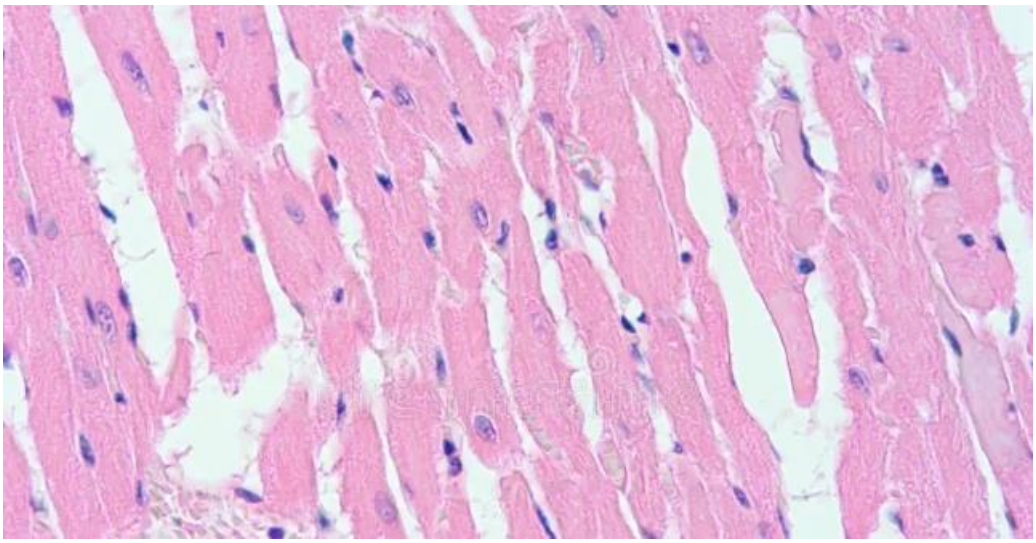


Figure 1. Ultrastructural changes in myocardial capillaries associated with peripartum cardiomyopathy. Electron microscopic examination demonstrates endothelial cell remodeling, structural abnormalities of the capillary wall, and narrowing of the vascular lumen. These morphological alterations reflect myocardial microvascular injury and impaired microcirculation.

Angiogenesis provides a second way to understand the microcirculatory abnormalities of PPCM. Myocardial capillaries are not static structures; they require continuous maintenance and repair. When factors supporting the endothelium are reduced, existing vessels may become more vulnerable and replacement of damaged microvessels may be insufficient. The available experimental work points to angiogenic imbalance rather than a single mechanical obstruction as an important mechanism of microvascular dysfunction.

Patten and colleagues examined the connection between angiogenic signaling and cardiac function. Their experiments showed that mice lacking cardiac PGC-1α, a regulator linked to vascular maintenance, developed severe peripartum cardiac dysfunction. Reduced microvascular density formed part of this experimental pattern. Importantly, treatment aimed at increasing angiogenic support improved the disease phenotype in that model. In the human component, women with PPCM had increased circulating sFLT1 levels, while sFLT1 was also associated with cardiac effects in experimental systems. These observations make an antiangiogenic environment a plausible contributor to myocardial vulnerability.

The biological role of sFLT1 is relevant because it can bind signaling molecules that would otherwise support vascular endothelial growth and survival. A rise in circulating antiangiogenic activity may weaken microvascular repair during a time of increased myocardial demand. However, the concentration of a circulating factor is not itself a histological measurement of capillary diameter, wall thickness, or endothelial cell loss. A tissue-based study would still be required to test whether patients with higher sFLT1 levels have more extensive structural damage in the myocardium. The prolactin-related hypothesis offers a complementary pathway. In the experimental work by Hilfiker-Kleiner and colleagues, an enzymatically cleaved prolactin fragment affected vascular integrity and contributed to the cardiac disease phenotype. The 16-kDa fragment was shown to have antiangiogenic and proapoptotic activity, providing a mechanism by which vascular injury may be connected to postpartum hormonal changes. Such findings support further study of endothelial survival and capillary stability during the peripartum period. They should not be simplified into the claim that all human PPCM is caused by this one hormone fragment.

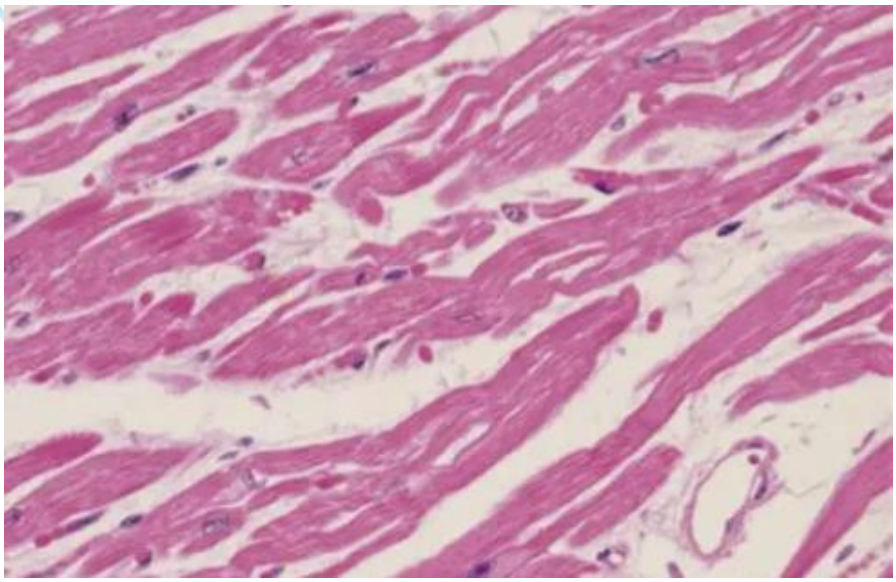


Figure 2. Morphological changes in the myocardial microvascular network associated with peripartum cardiomyopathy. Microscopic examination demonstrates reduced myocardial capillary density, decreased endothelial staining, and irregular distribution of small blood vessels. These alterations indicate impaired angiogenesis and structural remodeling of the myocardial microcirculation, which may contribute to reduced tissue perfusion and cardiac dysfunction.

In the present comparative synthesis, the evidence from ultrastructural studies and that from angiogenic experiments converged on the importance of the myocardial microvascular network, but the methods and populations differed. Direct biopsy observations show how injured vessels may look in human myocardium. Experimental studies show how specific pathways can disrupt or protect that network. These are related yet not interchangeable findings. Presenting them together helps explain the disease while preserving the limits of each study.

Pregnancy parity was considered as a separate clinical dimension. Clinical series have reported different distributions of PPCM among women with and without previous deliveries. A recent meta-analysis cited in the source thesis found an association between parity and PPCM risk. Nevertheless, the direction and clinical interpretation of the association depend on how parity was defined, which populations were included and how potential confounders were handled. The available studies did not supply matched myocardial biopsy measurements from primiparous and multiparous women.

It is therefore not possible to conclude from these sources that capillary lumen occlusion, endothelial apoptosis, microvessel density or perivascular fibrosis is definitely greater in one parity group. Factors such as maternal age, hypertension, pre-eclampsia, obesity, gestational history and the timing of tissue collection may influence both clinical risk and myocardial morphology. Differences attributed to repeated pregnancy would need to be evaluated against these factors before being interpreted as an independent parity effect.

From a morphological perspective, a future direct comparison should collect cardiac tissue using consistent criteria and record the anatomical location of every specimen. Routine staining could be used to examine myocyte architecture and interstitial tissue, while endothelial immunostaining could support estimates of capillary density. Where appropriate, CD31 or CD34 may help identify vascular profiles, provided staining quality and counting methods are standardized. Collagen-specific staining, including Masson trichrome, may demonstrate perivascular and interstitial fibrosis. Electron microscopy would allow more precise evaluation of endothelial ultrastructure in selected specimens.

Quantitative indicators could include capillary profiles per unit area, vascular lumen area, proportion of damaged endothelial cells, and the extent of perivascular collagen deposition. These indicators would need to be assessed using blinded sampling rules and interpreted alongside the interval from delivery, severity of left ventricular dysfunction, hypertensive disease, medications and other clinical factors. This suggested framework is a direction for further investigation; it was not applied to patient tissue in the present literature review.

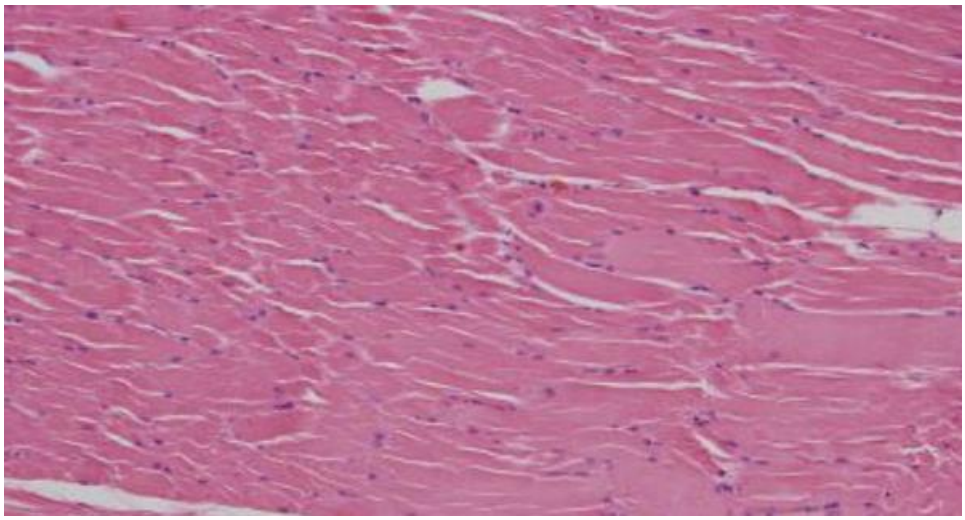


Figure 3. Pathomorphological changes in myocardial microvessels and surrounding interstitial tissue associated with peripartum cardiomyopathy. Microscopic examination demonstrates endothelial cell injury, narrowing of capillary lumina, irregular distribution of microvessels, and increased interstitial fibrosis. Collagen accumulation between cardiomyocytes and perivascular connective tissue remodeling indicate impaired myocardial microcirculation and progressive structural alterations of cardiac tissue.

The main practical result of the comparison is that PPCM should not be approached exclusively as a disease of cardiomyocyte contraction. Endothelial integrity and the supply of blood through small myocardial vessels may also shape tissue injury and recovery. Angiogenic mechanisms are especially relevant because they link the physiological demands of pregnancy with the local vascular response of the heart. At the same time, neither the presence of endothelial abnormalities nor a history of several deliveries should be treated as a sufficient explanation for an individual case without additional evidence.

This review has important limitations. It relies on a small set of publications with different methods, populations and aims. Some evidence is ultrastructural, some experimental and some clinical. No pooled morphometric analysis was possible. In particular, the lack of parity-stratified tissue measurements prevents direct comparison of first and subsequent pregnancies at the microscopic level. The strongest conclusion is therefore the relevance of myocardial microvascular pathology to PPCM and the need for a more precise comparative research design.

Conclusion

The reviewed studies show that myocardial microcirculatory abnormalities are relevant to peripartum cardiomyopathy. Reported structural changes include endothelial remodeling, capillary lumen abnormalities and injury to the surrounding myocardial interstitium. Such changes may disturb tissue perfusion and contribute to myocardial dysfunction.

Experimental evidence indicates that impaired angiogenic support, increased antiangiogenic activity and the effects of a cleaved prolactin fragment can damage myocardial microvascular networks. These mechanisms help explain the possible vascular contribution to PPCM, although their effects cannot be assumed to be identical in every patient.

Clinical literature suggests that pregnancy parity may influence the risk of PPCM. However, the available studies do not demonstrate a consistent difference in capillary density, endothelial injury or perivascular fibrosis between women with first and subsequent deliveries.

Future investigations should combine standardized myocardial histology, capillary morphometry, endothelial immunohistochemistry, and detailed reproductive and clinical histories. Such studies are needed to clarify whether parity independently influences myocardial microvascular pathology.

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