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PERIPARTUM CARDIOMYOPATHY: A COMPARATIVE ANALYSIS OF TWIN VERSUS SINGLETON GESTATIONAL RISKS: A NARRATIVE REVIEW

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ABSTRACT

Background. Peripartum cardiomyopathy is an idiopathic left ventricular systolic heart-failure syndrome presenting in late pregnancy or up to five months postpartum, with global incidence ranging from 1 per 1000–4000 births in North America and Europe to 1 per 100–300 in parts of sub-Saharan Africa. Multifetal gestation is a recurring risk factor, though its adjusted magnitude is uncertain.

Aim. To synthesise contemporary evidence on whether multifetal gestation constitutes an independent, mechanistically grounded PPCM risk factor.

Methods. A structured narrative review (January 2000–March 2026) of PubMed/MEDLINE, Scopus, and Web of Science records, supplemented by reference-list and guideline cross-referencing, including peer-reviewed primary studies, systematic or narrative reviews, and meta-analyses on PPCM epidemiology, hemodynamics, molecular biology, therapy, and prognosis in multifetal versus singleton gestations.

Results. A 2024 Finnish record-linkage study identified twin pregnancy as conferring an adjusted odds ratio of 2.74 (95% CI 1.37–5.49, $p = 0.005$) for peripartum heart failure, comparable to pre-eclampsia (aOR 2.43) (Puhakka et al., 2024). Twin gestation imposes 20% greater cardiac output, 15% greater stroke volume, and 13.5% greater left ventricular mass than singleton pregnancy, with progressive third-trimester loss of long-axis systolic efficiency (Kametas, 2003). A 2025 systematic review confirmed multifetal gestation as a recurrent risk factor across diverse cohorts (Dewi et al., 2025), corroborated by a 2022 global meta-analysis of over 7,000 cases from 41 studies (Hoevermann et al., 2022).

Conclusions. Multifetal gestation is an independent PPCM risk factor of comparable magnitude to pre-eclampsia, mediated by hemodynamic loading and amplified anti-angiogenic signalling on a genetic substrate (Davis et al., 2020). Incorporation of pregnancy plurality into stratified PPCM risk models is justified by this synthesis (Jackson et al., 2023).

KEYWORDS

Peripartum Cardiomyopathy, Pregnancy, Multiple, Heart Failure, Pre-Eclampsia, Risk Factors, Hemodynamics

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Research Objective

The primary objective of this review is to synthesize existing clinical and epidemiological data to determine whether the increased physiological load of twin gestations serves as an independent driver for the heightened incidence and severity of peripartum cardiomyopathy compared to singleton pregnancies. By systematically contrasting regional prevalence rates and clinical outcomes, this analysis seeks to bridge existing knowledge gaps regarding the role of hemodynamic stress in pregnancy-associated heart failure .

1. Introduction and Definition of PPCM

Peripartum cardiomyopathy is a rare form of left ventricular systolic heart failure that manifests during the final month of pregnancy or within the first five months postpartum, in the absence of alternative identifiable causes . Reported incidence ranges from approximately 1:1,300 to 1:15,000 pregnancies across global populations , with disproportionately higher rates observed in women of African ancestry and in those carrying multiple gestations . The condition frequently presents with non-specific symptoms—dyspnoea, fatigue, palpitations, or peripheral oedema—that overlap with the physiological cardiovascular adaptations of late pregnancy, contributing to a frequently documented delay in clinical recognition and to substantial maternal morbidity and mortality. Current evidence suggests that multifetal pregnancies impose a distinct hemodynamic burden, with some data identifying multiple gestations as an independent predictor of disease with an odds ratio of 2.76 .

Despite advances in echocardiographic and biomarker-based diagnosis, critical gaps persist regarding the precise aetiology, optimal surveillance strategies, and disease-specific therapies of PPCM . Among the established risk factors—advanced maternal age, multiparity, hypertensive disorders, and African ancestry—multifetal gestation has emerged as a particularly relevant but insufficiently characterised determinant . Physiological observations indicate that twin pregnancies impose a significantly greater haemodynamic load than singleton gestations, with larger plasma volume, higher cardiac output, increased placental mass, and reduced longitudinal myocardial contractility . However, integrated reviews that *specifically* compare the PPCM phenotype, the trajectory of left ventricular recovery, and the clinical implications of multifetal versus singleton pregnancies remain scarce .

The present narrative review aims to address this gap by systematically consolidating current epidemiological, haemodynamic, molecular, and therapeutic evidence on peripartum cardiomyopathy in twin versus singleton gestations, in order to clarify whether multifetal pregnancy constitutes an independent driver of maternal cardiovascular morbidity and to identify the implications for clinical surveillance and disease-specific management.

1.1. Hemodynamic Burden of Twin Pregnancies

This review aims to rigorously compare the incidence of PPCM in twin versus singleton pregnancies, given that the amplified physiological demands of multifetal gestations—including substantially increased plasma volume, cardiac output, and metabolic demands—likely modulate disease prevalence and clinical trajectory . This intensified physiological stress, further compounded by larger placental mass and heightened inflammatory responses, plausibly contributes to a higher incidence of PPCM in multifetal gestations . Indeed, a meta-analysis of 16 studies reported an average twin gestation rate of 9% among PPCM cases—threefold higher than the ~3% prevalence in the general population—providing compelling evidence of a strong association between multiple gestations and PPCM pathogenesis . Furthermore, clinicians should consider that the increased placental mass in twin pregnancies likely elevates the production of anti-angiogenic factors and

the 16-kDa N-terminal prolactin fragment, both of which are implicated in promoting cardiomyocyte apoptosis and myocardial dysfunction. Moreover, research indicates that multifetal pregnancies are associated with a reduced preload reserve and lower longitudinal systolic velocity compared to singleton gestations, potentially lowering the threshold for manifest heart failure. These hemodynamic findings are corroborated by recent clinical data showing an adjusted odds ratio of 2.74 for PPCM in patients carrying twins, reflecting the significant systemic strain inherent to multifetal pregnancy. Furthermore, this intensified systemic stress is frequently linked to a higher frequency of preeclampsia and hypertensive disorders, which are known to exacerbate maternal cardiac remodeling in twin pregnancies. Evidence suggests that twin pregnancies exhibit greater left ventricular dimensions and higher cardiac output than singletons, reflecting a distinct adaptation to increased volumetric load. Furthermore, the persistence of elevated cardiac output and reduced vascular resistance into the immediate postpartum period suggests a sustained cardiovascular strain that likely impairs the mother's ability to transition effectively to non-pregnant hemodynamics.

1.2. Multifetal Gestation as an Independent Epidemiological Risk Factor

Given this markedly elevated risk profile—and with twinning recognized as an established risk factor—it is essential to determine if twin pregnancies confer a significant independent risk for PPCM. Notably, advanced maternal age, multiparity, and gestational hypertension—well-established PPCM risk factors—occur with greater frequency in twin pregnancies. Specifically, multifetal gestations exhibit an adjusted odds ratio of 2.76 for developing the condition, underscoring that the hemodynamic burden of twins acts as an independent contributor to myocardial vulnerability. Furthermore, research indicates that the reduced preload reserve and altered longitudinal contractility observed in twin gestations may exacerbate this susceptibility, with evidence suggesting that myocardial recovery may be delayed in these patients compared to those with singleton pregnancies. Consequently, routine clinical screening for markers of heart failure is increasingly recommended for patients carrying multiple fetuses to facilitate earlier intervention in this high-risk population. Advanced cardiac monitoring, including serial echocardiography and natriuretic peptide assessment, is essential during the peripartum window, as twin gestations show higher postpartum indices of left atrial volume and E/e' compared to singleton pregnancies.

1.3. Postpartum Biomarkers and Cardiac Remodelling

The heightened susceptibility to heart failure in the immediate postpartum period is further underscored by data indicating that twin pregnancies exhibit significantly higher left atrial volume indices and elevated natriuretic peptide levels compared to singleton counterparts. These hemodynamic alterations are compounded by the larger placental volume characteristic of multiple gestations, which induces a more pronounced secretion of antiangiogenic factors such as sVEGFR1 that are hypothesized to impair myocardial microvasculature. This increased placental burden leads to significantly elevated systemic concentrations of soluble fms-like tyrosine kinase-1 (sFlt1), which serves as a potent cardiotoxic mediator that contributes to the pathogenesis of PPCM. Furthermore, the convergence of these angiogenic imbalances and existing pre-existing maternal risk factors, such as advanced age and prior hypertensive disorders, creates a synergistic effect that potentially lowers the threshold for myocardial failure. Recent evidence demonstrates that women with twin pregnancies exhibit significantly higher BNP/NT-proBNP levels and increased E/e' ratios within the first week postpartum, highlighting a critical window of elevated myocardial strain during the immediate transition after childbirth.

1.4. Compounding Cardiovascular Burden: Preeclampsia and Postpartum Load

Pre-eclampsia and twin gestation are not merely concurrent risk factors in peripartum cardiomyopathy; in mechanistic terms they operate along parallel physiological axes whose combined effect is approximately additive at the epidemiological level and plausibly synergistic at the molecular level.

The independent contribution of twin gestation to pre-eclampsia risk was quantified in the Adank prospective population-based cohort study of 91 women with twin pregnancies and 8107 women with singleton pregnancies, in which women with twin pregnancies were more likely to develop pre-eclampsia with an odds ratio of 3.63 (95% CI 1.76–7.48). In the same cohort, soluble fms-like tyrosine kinase-1 and placental growth factor concentrations were both higher in early (13.4 weeks) and mid-pregnancy (20.4 weeks) in women with twin pregnancies than in those carrying singletons, indicating that the anti-angiogenic state that defines pre-eclampsia is present at a higher set-point in twin gestations long before the clinical syndrome manifests. This mechanistic superposition is corroborated by the contemporary NOAM Score derivation cohort of 317,892

deliveries analysed by Shmueli and colleagues, in which pre-eclampsia conferred an adjusted odds ratio of 7.50 (95% CI 4.69–11.7) for PPCM — the largest single risk-factor signal in that multivariable model and approximately 2.7-fold greater than the multifetal-pregnancy signal of 2.76 (95% CI 1.36–5.07) within the same regression. The 2024 Finnish population-based record-linkage study placed pre-eclampsia close to twin pregnancy in the peripartum heart-failure risk hierarchy (aOR 2.43, 95% CI 1.39–4.23, $p = 0.002$ versus twin pregnancy aOR 2.74, 95% CI 1.37–5.49, $p = 0.005$), supporting the interpretation that the two conditions are separate, partially collinear, but independently contributory insults.

On the hemodynamic axis, twin gestation already imposes a third-trimester profile of elevated afterload sufficient to increase mean arterial pressure from approximately 2% below singleton values in the first trimester to 3% above singleton values at term ($p = 0.03$), with long-axis shortening simultaneously falling from 6.5% above singleton values to 3% below singleton values. Pre-eclampsia adds a steeper pressure-load ramp to this substrate. Umazume and colleagues documented in their longitudinal cohort of 44 singleton and 22 twin pregnancies that women with twin pregnancies had significantly smaller second-trimester inferior vena cava diameters and significantly higher third-trimester creatinine levels than those with singleton pregnancies — markers of reduced venous capacitance and altered renal-volume handling that are exaggerated further when pre-eclampsia co-exists. Within the first postpartum week the same authors observed significantly higher brain natriuretic peptide and left atrial volume index values in the twin-pregnancy group, with BNP positively correlated with left atrial volume index ($\beta = 0.49$, $p < 0.01$) and E/e' ($\beta = 0.41$, $p < 0.01$); in singleton pregnancies both immediately-postpartum BNP and NT-proBNP correlated negatively with later E/e' at one month, suggesting a graded transitional diastolic recovery that is plausibly attenuated or absent in twin pregnancies and further attenuated when pre-eclampsia is superimposed. Zekert and colleagues extended the hemodynamic observation into the postpartum window, demonstrating that the prolonged elevation of cardiac output and reciprocal reduction in total vascular resistance persist into the late postpartum period in uncomplicated twin pregnancies, indicating an incomplete transition to non-pregnant cardiovascular physiology. Pellegrino and colleagues further demonstrated that left-ventricular compliance is enhanced, not reduced, in twin pregnancy — a finding that places the eventual decompensation in twin-PPCM in a distinct hemodynamic category from pre-eclamptic cardiac dysfunction, where compliance is reduced and afterload is increased.

On the molecular axis, the convergence of twin and pre-eclamptic pathophysiology is best framed as a third potential hit layered on the two-hit vascular-hormonal model of PPCM. The enhanced placental mass of twin pregnancies increases the absolute systemic secretory capacity for sFlt1, and pre-eclampsia further upregulates placental sFlt1 release, producing circulating sFlt1 levels that increase exponentially toward birth and that are documented to be elevated in women with PPCM and to correlate with disease severity and adverse events. In cardiac-specific PGC-1 α -deficient mice, exogenous sFlt1 is sufficient to cause profound systolic dysfunction even in non-pregnant animals, indicating that the anti-angiogenic load of twin gestation plus pre-eclampsia can quantitatively exceed the threshold at which host susceptibility translates into manifest disease. The Haghighia biomarker cohort provided complementary human evidence: sFlt1 levels remained elevated postpartum in women whose pregnancies were complicated by hypertensive disorders and correlated with subsequent PPCM presentation, indicating that pre-eclampsia-complicated twin pregnancies constitute the highest anti-angiogenic-load stratum within the peripartum population. Bandyopadhyay and colleagues highlighted the prolactin-derived vasoinhibin fragment as a further pro-inflammatory, anti-angiogenic, and pro-apoptotic mediator that restricts myocardial oxygen and nutrient supply — converging on the same end-organ vulnerability that the two-hit model invokes.

Clinically, this superposition mandates differentiated surveillance. The ANGIOCOR prospective cohort protocol designed by Ullmo and colleagues explicitly seeks to characterise cardiac dysfunction and remodelling regulated by the anti-angiogenic environment in pre-eclamptic patients through serial echocardiographic and biomarker phenotyping, providing the methodological template that future twin-pregnancy cohorts with pre-eclampsia should replicate. Until such stratified data are available, the convergent signal from Adank, Shmueli, and Puhakka supports the operational recommendation that women with twin pregnancies who develop any hypertensive disorder in the third trimester — gestational hypertension, pre-eclampsia, or chronic-hypertension-with-superimposed-pre-eclampsia — should receive the most intensive surveillance protocol within the peripartum-care pathway, including third-trimester echocardiography, postpartum natriuretic peptide measurement, and explicit counselling regarding early postpartum symptom reporting.

1.5. The Two-Hit Pathophysiological Model

Beyond these hemodynamic stressors, the exaggerated placental secretion of sFlt1 in multiple gestations directly promotes an anti-angiogenic environment that significantly exacerbates susceptibility to myocardial injury. This anti-angiogenic milieu is further compounded by a deficiency in transcriptional coactivators like PGC-1 α , which, when coupled with the heightened metabolic demands of multiple gestations, impairs the heart's angiogenic and contractile reserves. Concurrent with these angiogenic perturbations, the altered processing of prolactin by cathepsin D into its 16 kDa pro-apoptotic isoform represents an additional molecular mechanism triggered by this anti-angiogenic stress. Elevated serum levels of this cleaved prolactin fragment further drive myocardial damage and endothelial dysfunction, directly correlating with the severity of cardiac failure observed in these pregnancies.

1.6. Therapeutic Strategies: Bromocriptine and Acute Stabilisation

Given this molecular cascade, current therapeutic strategies increasingly incorporate bromocriptine to inhibit further prolactin cleavage, alongside standard heart failure protocols to mitigate the secondary damage exacerbated by this intense anti-angiogenic environment. Moreover, early clinical stabilization in this high-risk subset is critical, as severe forms of the disease may necessitate advanced mechanical circulatory support to bridge patients toward potential myocardial recovery. Despite these interventions, clinicians must remain alert to the risk of thromboembolic events and malignant arrhythmias during the acute phase, as the unpredictable nature of cardiac recovery in multifetal gestations may warrant prolonged surveillance. Long-term follow-up is particularly important given that the 16-kDa prolactin fragment's pro-apoptotic effects on cardiomyocytes may complicate the timeline for functional improvement. In addition to medical management, identifying markers of diastolic dysfunction through serial echocardiography remains essential, as evidence suggests that reduced longitudinal contractility and impaired systolic function can persist well into the postpartum period. This molecular pathway is further validated by the observation that elevated baseline prolactin levels correlate with poorer clinical outcomes in patients presenting with severely reduced left ventricular ejection fraction. Consequently, pharmacological blockade of prolactin signaling represents a targeted intervention that may attenuate this cascade by preventing the production of the cardiotoxic 16 kDa fragment, thereby fostering endothelial preservation and myocardial recovery. However, as clinical evidence regarding the efficacy of bromocriptine remains heterogeneous, its application should be tailored to individual patient profiles, carefully weighing the potential for cardiac recovery against the implications for breastfeeding. Beyond the use of bromocriptine, research into alternative therapeutic strategies is urgently required, as current management remains largely restricted to standard heart failure pharmacotherapy. Furthermore, future investigations must prioritize longitudinal studies to better define the long-term prognosis of PPCM survivors, specifically focusing on the cumulative impact of recurrent pregnancy and subsequent cardiovascular disease risk. Integrating advanced imaging modalities, such as speckle strain analysis and three-dimensional echocardiography, will be pivotal in detecting subtle myocardial changes that precede overt clinical failure in this high-risk demographic. Finally, the identification of genetic predispositions, such as titin-truncating variants, may further refine risk stratification strategies and inform clinical management. Ultimately, the synthesis of molecular, hemodynamic, and genetic data will broaden our understanding of PPCM and optimize personalized treatment strategies. Developing comprehensive screening protocols that incorporate these multivariable predictors could significantly reduce the morbidity associated with this disease by allowing for pre-emptive management before irreversible ventricular remodeling occurs.

1.7. Genetic Predisposition and Risk Stratification

Beyond these acute interventions, the integration of genetic screening for variants such as titin-truncating mutations is becoming increasingly pertinent, as underlying genetic predispositions may modulate the individual threshold for symptomatic heart failure in the presence of multiple gestation stressors. Ultimately, understanding the intersection of these genetic, hormonal, and hemodynamic factors is essential for developing predictive diagnostic models that can identify women at the highest risk of progression before clinical decompensation occurs. Future prospective studies are required to validate whether targeted biomarker surveillance—including serial monitoring of the sFlt-1/PlGF ratio and 16 kDa prolactin levels—can effectively guide personalized management strategies for patients with twin gestations. Furthermore, establishing standardized protocols for longitudinal follow-up in this specific population may assist in distinguishing between reversible physiological remodeling and the early subclinical markers of persistent myocardial dysfunction. Specifically, determining whether the sustained proteolytic activity of cathepsin D persists in the

months following delivery could provide critical prognostic value regarding clinical outcomes in PPCM patients. Given the heterogeneity of the disease, implementing multi-marker diagnostic strategies is essential to enhance clinical accuracy and refine the therapeutic management of these high-risk patients. Establishing longitudinal assessments through serial transthoracic echocardiography may prove instrumental in identifying premature parameters that distinguish maladaptive cardiovascular responses in twin pregnancies from those observed in singleton gestations.

1.8. Future Directions: Registries, Biomarkers and Precision Medicine

Future research should specifically aim to quantify the relative contributions of these placental, genetic, and environmental factors to distinguish between physiological cardiac adaptation and early maladaptive signaling. By delineating these specific biomarkers and physiological thresholds, clinicians can better stratify the monitoring frequency required for patients with twin pregnancies, potentially mitigating the morbidity associated with this condition. Additionally, investigating the longitudinal efficacy of bromocriptine therapy in the specific context of multiple gestations may provide critical insights into whether early endocrine modulation can attenuate the heightened risk of long-term myocardial impairment. Establishing comprehensive registries that categorize patients by pregnancy plurality will be essential to validate these therapeutic observations and standardize clinical management protocols. Furthermore, incorporating multimodality imaging, such as speckle-tracking echocardiography, into standardized follow-up protocols may facilitate the earlier detection of subclinical myocardial dysfunction in these high-risk cohorts. These prospective longitudinal assessments are vital to characterizing how an anti-angiogenic environment drives long-term cardiac remodeling and influences future cardiovascular disease risk. By employing multi-marker strategies that integrate these imaging data with biomarker profiles, clinicians can enhance the diagnostic accuracy of PPCM and tailor interventions to address the unique heterogeneity observed in twin versus singleton pregnancies. Ultimately, a multidisciplinary care framework that incorporates social support and community resources is essential for managing this patient population, as the psychosocial burden often parallels the clinical severity of the cardiac diagnosis. Furthermore, prioritizing the establishment of international registries will be imperative for collecting high-fidelity prospective data, which remains essential to elucidating the disease-specific biomarkers and pathophysiological nuances of this condition. Additionally, future investigations must prioritize the exploration of circulating microparticles and their role in early disease detection, as these biological markers may serve as sensitive indicators of cardiac structural alterations prior to the onset of overt heart failure. Integrating these advanced diagnostic modalities into routine obstetric care may allow for the timely implementation of targeted interventions, potentially shifting the paradigm from reactive crisis management to proactive, preventative care. Such advancements would likely be complemented by large-scale omics investigations, which hold the potential to identify the key molecular drivers and pathways contributing to this multifactorial condition. Moreover, these high-dimensional datasets could facilitate the development of prognostic scoring tools, enabling clinicians to identify patients likely to benefit from early, tailored pharmacological stabilization.

2. Discussion

The objective of this narrative review was to systematically consolidate current epidemiological, hemodynamic, molecular, and therapeutic evidence on peripartum cardiomyopathy in twin versus singleton gestations, with the aim of clarifying whether multifetal pregnancy constitutes an independent driver of maternal cardiovascular morbidity. The findings assembled across the preceding nine sections converge toward a consistently affirmative answer, while simultaneously exposing important gaps in the available evidence base that warrant explicit acknowledgment. Primarily, the scarcity of large-scale, prospective comparative studies precludes definitive quantification of the incremental risk imposed by twin gestations compared to singleton cohorts.

2.1. Quantification of Risk: The Twin Gestation Signal

The contemporary epidemiological case that twin gestation is an independent risk factor for peripartum cardiomyopathy rests on three converging datasets and a mechanistic substrate that links each of them to the clinical phenotype.

In the 2024 Finnish population-based record-linkage study by Puhakka and colleagues, derived from 432 incident peripartum heart-failure cases identified through mandatory national hospital and mortality

registers, twin pregnancy conferred an adjusted odds ratio of 2.74 (95% CI 1.37–5.49, $p = 0.005$) for peripartum heart failure after multivariate adjustment for maternal age, parity, body-mass index, pregestational diabetes, chronic hypertension, and preeclampsia. The magnitude of this signal places multifetal gestation in the same risk stratum as preeclampsia (aOR 2.43, 95% CI 1.39–4.23, $p = 0.002$) and second only to pregestational diabetes (aOR 3.27, 95% CI 1.66–6.45, $p < 0.001$) within the same multivariable model. Maternal pre-pregnancy BMI ≥ 35 kg/m² (aOR 2.04, 95% CI 1.28–3.25, $p = 0.003$), prior hypertensive disorder of pregnancy (aOR 2.44, 95% CI 1.22–4.88, $p = 0.012$), and gestational hypertension without significant proteinuria (aOR 2.14, 95% CI 1.27–3.61, $p = 0.004$) were each independently associated with peripartum heart failure, confirming that the twin-pregnancy signal persists after adjustment for these established metabolic and hypertensive covariates rather than being explained by their co-prevalence.

The Finnish population-level signal is reinforced by the 2025 systematic review and meta-analysis of Dewi and colleagues, in which multifetal pregnancy was associated with a significantly higher pooled incidence of peripartum cardiomyopathy than singleton pregnancy across the included studies, with effect-size heterogeneity attributable to differential inclusion of preeclampsia-complicated multifetal gestations in the source cohorts. The parallel 2022 global meta-analysis by Hoevelmann and colleagues, encompassing more than 7000 PPCM cases from 41 studies, identified multifetal pregnancy as one of the recurrently reported risk factors in unadjusted analyses across regions; the geographic spread of this signal — across North American, European, sub-Saharan African, and South Asian cohorts — argues against a population-specific artefact and supports a biologically generalisable effect.

Independent confirmation at the cohort level derives from the Adank prospective population-based study of maternal cardiovascular adaptation in twin pregnancy, in which longitudinal echocardiographic and hemodynamic profiling documented the magnitude of the gestational cardiovascular load: the 20% greater maternal cardiac output, 15% greater stroke volume, 3.5% higher heart rate, and 13.5% greater left ventricular mass documented by Kametas and colleagues across 119 twin pregnancies compared with 128 singleton controls quantify the precise hemodynamic insult that the peripartum heart must accommodate. Within this same Adank cohort, late-pregnancy loss of long-axis shortening — from 6.5% above singleton values in the first trimester to 3% below singleton values by term ($p = 0.01$) — maps onto the critical window in which peripartum cardiomyopathy most often presents clinically.

Mechanistic coherence between the epidemiological and hemodynamic signals is provided by the two-hit vascular-hormonal model: the larger placental mass in twin pregnancies increases systemic sFlt1 secretion (particularly when compounded by preeclampsia), and the simultaneously greater circulating volume and cardiac demand accelerate the transition from compensated to decompensated peripartum cardiac function in genetically susceptible women. The recent 20-year population study of PPCM by Jackson and colleagues confirmed both the temporal stability of the diversity of identified risk factors and the magnitude of the racial disparity in outcomes that should be interpreted alongside the multifetal-gestation signal rather than in isolation.

Three caveats temper the strength of this quantification. First, none of the contemporary multivariable models have stratified plurality within a preeclampsia cohort; full mechanistic decomposition of the twin-pregnancy signal into hemodynamic versus anti-angiogenic components therefore remains incomplete. Second, the predominantly cross-sectional design of the twin-pregnancy echocardiographic literature limits causal inference about the trajectory of subclinical cardiac impairment. Third, the global meta-analysis documents substantial heterogeneity in recovery and outcome measures across regions, suggesting that the magnitude of the signal — rather than its direction — may vary with case-ascertainment practice and access to bromocriptine-augmented heart-failure therapy.

2.2. Pathophysiological Convergence: The Two-Hit Model Amplified

The "two-hit" hypothesis proposed by the European Society of Cardiology study group on PPCM posits that a systemic anti-angiogenic state—typically driven by late-pregnancy cleavage of prolactin into its 16-kDa pro-apoptotic fragment and by placental secretion of soluble fms-like tyrosine kinase-1 (sFlt1)—converges with a host susceptibility factor, most prominently deficiency of the cardioprotective transcriptional coactivator PGC-1 α . Twin pregnancies appear to amplify both limbs of this model simultaneously. On the hemodynamic side, the larger plasma volume, augmented cardiac output, larger placental mass, and reduced preload reserve documented in twin gestations generate a sustained mechanical stimulus that approaches—and in some cases exceeds—the limits of physiological cardiac adaptation. On the molecular side, the disproportionately enlarged placenta characteristic of multiple gestations produces markedly elevated

concentrations of sFlt1 and anti-angiogenic mediators and, under conditions of oxidative stress, drives the cathepsin D-mediated cleavage of prolactin into its cardiotoxic 16-kDa isoform. The convergence of these two amplified pathways offers a plausible mechanistic explanation for the multifold increased PPCM incidence in twin pregnancies observed in the epidemiological data.

A further consideration is the frequent coexistence of pre-eclampsia in multifetal gestations, which independently contributes anti-angiogenic and endothelial-dysregulatory stimuli that may further sensitize the maternal myocardium to peripartum hemodynamic overload.

2.3. Clinical Translation: Surveillance, Therapeutic Targeting, and Risk Stratification

The mechanistic synthesis indicates that women with twin pregnancies represent a clearly identifiable, high-risk subgroup in whom targeted cardiovascular surveillance may yield clinically meaningful benefit. Current guidance from the Heart Failure Association of the European Society of Cardiology recommends bromocriptine as a disease-specific adjunct on the basis of its blockade of prolactin cleavage, with a class IIb, level of evidence B recommendation. The recent updated meta-analysis by Lueg and colleagues reported a significantly higher probability of LVEF recovery with bromocriptine added to standard therapy (OR = 2.8, $p = 0.03$), with a trend toward lower all-cause mortality (OR = 0.61, $p = 0.16$) that did not reach statistical significance. These findings support the rationale for considering early bromocriptine initiation specifically in patients with twin gestations and severely reduced LVEF, although no RCT to date has stratified outcomes by pregnancy plurality. The German randomized trial of prolonged bromocriptine in acute PPCM and the recent observational cohort from Haghikia and colleagues provide additional supportive evidence, while also highlighting interindividual variability in prolactin levels and treatment response.

Concurrently, the integration of advanced echocardiographic modalities—including speckle-tracking strain analysis and three-dimensional imaging—promises earlier detection of subclinical myocardial dysfunction in this population. Titin-truncating and other genetic variants have been identified in up to 20% of PPCM cases, raising the possibility that genetic screening could further refine individual risk estimation in women with twin pregnancies. The recent establishment of national and international registries—including the ESC EUROBS program and the proposed Italian multi-omics registry—offers a critical infrastructure for generating the higher-quality, plurality-stratified data needed to translate these mechanistic insights into evidence-based clinical algorithms.

2.4. Clinical Implications and Future Directions

From a clinical standpoint, three implications emerge. First, women with twin pregnancies should be regarded as a high-risk cohort in whom a low threshold for symptom evaluation and proactive echocardiographic surveillance is justified, particularly in the late third trimester and the early postpartum period. Second, the additive hemodynamic and molecular burden characteristic of multiple gestations supports a lower threshold for early bromocriptine consideration in PPCM cases with severely reduced LVEF, with concurrent prophylactic anticoagulation as recommended regardless of treatment allocation. Third, future research must move beyond the binary twin-versus-singleton classification and incorporate within-plurality stratification by chorionicity, pre-eclampsia status, and genetic susceptibility, while leveraging multi-marker panels integrating imaging and circulating biomarkers.

In conclusion, the synthesized evidence supports the inference that multifetal gestation is a clinically meaningful and mechanistically plausible independent risk factor for peripartum cardiomyopathy, predominantly through the convergence of intensified hemodynamic stress with an amplified anti-angiogenic placental milieu. Targeted surveillance protocols and earlier consideration of prolactin-blocking therapy constitute actionable next steps toward reducing maternal morbidity in this population.

3. Limitations

Several limitations should be considered when interpreting the evidence base for peripartum cardiomyopathy in multifetal gestation.

First, the mechanistic foundation of the two-hit model rests predominantly on murine experiments in which cardiac-specific STAT3 knock-out or PGC-1 α deletion drive postpartum systolic dysfunction through oxidative-stress-mediated cleavage of prolactin into a 16-kDa vasculotoxic fragment. Human prolactin is more resistant to cathepsin-D cleavage than rodent prolactin, and quantitative translation of the murine 16-kDa prolactin axis to human PPCM must therefore be made with caution. The complementary PGC-1 α model, which implicates placental anti-angiogenic sFlt1 excess, has direct human correlate data: exogenous sFlt1 administration reproduces systolic dysfunction in PGC-1 α -deficient mice even in non-pregnant animals, and circulating sFlt1 levels are elevated in a subset of human PPCM cases and predict worse outcomes — but the absolute predictive value of sFlt1 in unselected populations remains modest.

Second, the largest contemporary epidemiological dataset on multifetal pregnancy as a risk factor for PPCM (the Finnish population-based record-linkage study, $n = 432$ incident peripartum heart-failure cases) reports an adjusted odds ratio of 2.74 (95% CI 1.37–5.49, $p = 0.005$) for twin gestation but cannot establish unambiguously whether this signal reflects the additional hemodynamic and anti-angiogenic load of twin pregnancy itself, or merely the disproportionately higher co-prevalence of preeclampsia in twin gestations (aOR 2.43, 95% CI 1.39–4.23 in the same dataset). Adjustment models cannot fully capture this collinearity, and a definitive mechanistic decomposition would require prospective stratification by plurality within a preeclampsia cohort.

Third, registry data — including the Investigations of Pregnancy-Associated Cardiomyopathy cohort from which the contemporary estimates of recovery and racial disparity in outcome derive — depend on diagnostic criteria that have evolved substantially over the past 20 years; the most recent analyses document LVEF recovery rates of approximately 70% at 12 months, but this denominator is influenced by variable exclusion of women lost to follow-up, differential access to guideline-directed heart-failure therapy, and heterogeneous thresholds for defining recovery. The Hoevelmann 2022 global meta-analysis of more than 7000 cases from 41 studies similarly highlights that case ascertainment, baseline LVEF cut-offs and recovery definitions vary internationally, and pooled estimates should be interpreted as approximate rather than precise.

Fourth, cardiac-function data on twin pregnancies — including the foundational cross-sectional study by Kametas and colleagues and the longitudinal cohort by Ghi and colleagues — are derived predominantly from normotensive, uncomplicated twin gestations and cannot be extrapolated to the preeclampsia-complicated twin pregnancy most relevant to the PPCM discussion. Impaired long-axis shortening at term and reduced diastolic compliance are observed even in uncomplicated twin pregnancies, but the additive effect of preeclampsia on these parameters remains incompletely quantified.

Fifth, the genetic predisposition evidence carries two methodological caveats. While 15% of unselected PPCM patients harbour DCM-associated truncating variants identified by a 43-gene panel, predominantly in the A-band region of TTN, and IPAC post-hoc analyses correlate these variants with lower 12-month LVEF, more than 90% of TTN truncating-variant carriers do not develop PPCM, indicating that the genetic contribution is necessary but not sufficient. The Jackson 20-year population study confirmed the 15% TTN-prevalence figure and emphasised that genetic testing is not yet routine in resource-constrained settings, limiting external validity.

Sixth, the therapeutic evidence base for bromocriptine in PPCM remains dominated by small mechanistic trials and observational comparisons. The rational multicentre trial by Haghikia and colleagues ($n = 80$ randomised) provided the prospective bromocriptine regression data; an updated meta-analysis incorporating recent additions continues to favour bromocriptine addition over standard heart-failure therapy alone, but heterogeneity in dosing regimens (1-week versus 8-week), small individual trial sizes, and the absence of prespecified genomic stratification constrain the strength of any pooled inference.

Finally, racial disparity in PPCM outcome — particularly the elevated incidence and reduced recovery rate documented in women of African descent — appears consistently across registries including IPAC, the African Pregnancy-Associated Cardiomyopathy registry, and the global meta-analysis, but disentangling biological from socioeconomic determinants remains methodologically challenging in observational data. Until dedicated prospective studies designed to disaggregate these factors are completed, clinicians should interpret race-stratified outcomes as population-level signals rather than individual-level prognostic markers.

4. Conclusions

On the basis of the epidemiological, hemodynamic, molecular, and therapeutic evidence synthesized in this narrative review, the following conclusions can be drawn regarding the relationship between twin gestation and peripartum cardiomyopathy:

Twin pregnancy constitutes a clinically meaningful and mechanistically plausible independent risk factor for PPCM. Pooled evidence from a meta-analysis of 16 studies indicates a multifetal gestation rate of approximately 9% among PPCM cohorts—threefold higher than the ~3% background prevalence in the general obstetric population. Registry-level data corroborate this signal with an adjusted odds ratio of 2.74–2.76 for PPCM in twin pregnancies, supporting the clinical relevance of multifetal gestation as a stratification variable.

The "two-hit" pathophysiological model is plausibly amplified in multifetal gestations. The convergence of intensified hemodynamic stress—elevated plasma volume, cardiac output, placental mass, and reduced preload reserve documented in twin pregnancies,—with the disproportionately large placental secretion of anti-angiogenic mediators (sFlt1, soluble VEGF receptor-1) and the cathepsin D-mediated cleavage of prolactin into its 16-kDa pro-apoptotic isoform, provides a coherent mechanistic framework for the disproportionate PPCM incidence observed in this population.

The frequent coexistence of pre-eclampsia in multifetal gestations further compounds maternal cardiovascular risk, introducing an additional anti-angiogenic and endothelial-dysregulatory stimulus that may sensitize the maternal myocardium to peripartum hemodynamic overload. This interaction warrants explicit consideration in the clinical assessment of women with twin pregnancies who develop hypertensive disorders in the third trimester.

A low clinical threshold for proactive cardiovascular surveillance is justified in twin pregnancies. Targeted protocols—including serial echocardiography with strain analysis, natriuretic peptide measurement, and blood pressure monitoring from the late third trimester through the early postpartum period—represent the most readily actionable next step for mitigating morbidity in this identifiable high-risk cohort.

Bromocriptine merits earlier consideration in twin pregnancies complicated by severe LV dysfunction, on the basis of its mechanism-specific blockade of prolactin cleavage and the consistent—albeit not yet trial-confirmed in plurality-stratified analyses—signal of improved LVEF recovery (OR = 2.8; $p = 0.03$) reported in the updated meta-analysis. The prospective randomized German trial of prolonged bromocriptine and the contemporary European position statement provide additional supporting rationale, while highlighting the need for pregnancy-plurality-specific subanalyses.

Pregnancy-plurality-specific prospective registries are essential to advance the field. The available evidence remains constrained by heterogeneous diagnostic criteria across study periods, residual confounding from co-occurring risk factors such as advanced maternal age and fertility treatment, and the absence of RCT-level data dedicated to twin pregnancies. The recent establishment of the ESC EUROBS program and the proposed Italian multi-omics PPCM registry, together with the NOAM risk score, constitute the critical infrastructure through which the mechanistic hypotheses advanced in this review can be translated into validated, evidence-based clinical protocols.

In aggregate, the convergence of amplified hemodynamic, anti-angiogenic, and clinical risk signals indicates that women with twin pregnancies should be regarded as a distinct high-risk cohort within peripartum cardiology. Targeted surveillance and consideration of prolactin-blocking therapy, as well as awareness of pregnancy plurality in risk assessment, are potential strategies for reducing maternal morbidity and mortality in this population.

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