Peripartum cardiomyopathy

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Peripartum cardiomyopathy (PPCM) is a disorder in which initial left ventricular systolic dysfunction and symptoms of heart failure occur between the late stages of pregnancy and the early postpartum period. It is common in some countries and rare in others. The causes and pathogenesis are poorly understood. Molecular markers of an inflammatory process are found in most patients. Clinical presentation includes usual signs and symptoms of heart failure, and unusual presentations relating to thromboembolism. Clinicians should consider PPCM in any peripartum patient with unexplained disease. Conventional heart failure treatment includes use of diuretics, β blockers, and angiotensin-converting enzyme inhibitors. Effective treatment reduces mortality rates and increases the number of women who fully recover left ventricular systolic function. Outcomes for subsequent pregnancy after PPCM are better in women who have first fully recovered heart function. Areas for future research include immune system dysfunction, the role of viruses, non-conventional treatments such as immunosuppression, immunoadsorption, apheresis, antiviral treatment, suppression of proinflammatory cytokines, and strategies for control and prevention.

Peripartum cardiomyopathy (PPCM) is a disorder of unknown cause in which initial left ventricular systolic dysfunction and symptoms of heart failure occur between the last month of pregnancy and the first 5 months postpartum.[1,2] Elkayam and colleagues[3] described an identical clinical condition that appeared earlier in pregnancy; these women (n=23) were diagnosed with "pregnancy-associated" cardiomyopathy at 17–36 weeks of gestation, and did not differ clinically from women with the usual presentation of PPCM (n=100). Some reports of PPCM[4–6] also include women who presented with first heart failure in the sixth month postpartum. All these conditions might be part of the same clinical entity, with an expanded time interval for onset of heart failure.

An essential element in diagnosis of PPCM is the demonstration of left ventricular systolic dysfunction. Because echocardiography was not available at the time of Demakis' original description of the condition,[1] specific echocardiographic measures of left ventricular systolic dysfunction have been proposed as additional criteria.[7] These measures include an ejection fraction of less than 45%, fractional shortening of less than 30%, or both, and end-diastolic dimension of greater than 2·7 cm/m² body surface-area. The need for echocardiographic confirmation of left ventricular systolic dysfunction often presents a difficulty in developing countries where the necessary technology is not available. However, even in settings of poverty, echocardiographic strategies have been shown to be possible and practical.[8,9]

PPCM remains a diagnosis of exclusion. No additional specific criteria have been identified to allow distinction between a peripartum patient with new onset heart failure and left ventricular systolic dysfunction as PPCM and another form of dilated cardiomyopathy. Therefore, all other causes of dilated cardiomyopathy with heart failure must be systematically excluded before accepting the designation of PPCM. Recent observations from Haiti[10] suggest that a latent form of PPCM without clinical symptoms might exist. The investigators identified four clinically normal postpartum women with asymptomatic systolic dysfunction on echocardiography, who sub-sequently either developed clinically detectable dilated cardiomyopathy, or improved and completely recovered heart function.

Epidemiology

Although it seems likely that women of reproductive age all over the world have some risk of developing PPCM, good data about incidence are unavailable because so few population-based registries exist. Recent reports suggest an estimated incidence of one case per 299 livebirths in Haiti,[11] one case per 1000 livebirths in South Africa,[12] and one case per 2289 livebirths[13] to one case per 4000 livebirths in the USA.[2] These more recent data from the USA suggest a higher incidence than reported in earlier studies.[14,15] The reasons for this variation in incidence between countries remain unknown.

Cases of PPCM that adhere to the stated diagnostic criteria probably represent a similar disease, despite geographical variation in contributing factors. The remarkable propensity for recovery of left ventricular function observed in the diverse locations provides further evidence for a similar disease process. It should not be surprising that varying genetic pools and diverse environmental factors play parts of varying importance

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Search strategy and selection criteria

We aimed to summarise the results of a MEDLINE search (January, 1960, to January, 2006) on the current understanding of the epidemiology, aetiology, clinical profile, and management of PPCM. We used the search terms "peripartum cardiomyopathy", "postpartum cardiomyopathy", "heart failure in pregnancy", and "heart failure postpartum". We also searched the reference lists of articles identified by this strategy and selected those we judged relevant. Several review articles and book chapters were included because they provided comprehensive overviews. We identified areas in which knowledge is deficient and where molecular research efforts should be directed in seeking to understand the basic pathogenesis of PPCM.

	Haiti, 2005[8,11] (n=98)*	South Africa, 2005[9,21] (n=100)*	USA, 2005[3] (n=100)†	USA, 1971[1,22] (n=27)‡
Age (years)	31·8 (8·1, 16–51)	31·6 (6·6, 18–45)	30·7 (6·4, 16–43)	14 patients >30, 13 patients <30
Gravidity	4·3 (1–10)	3 (1–7)	2·6 (1–10)	8 patients (29%) G1–2, 19 patients (71%) >G3
Primigravidas	24 (24·5%)	20 (20%)	37 (37%)	8 (29%)§
Hypertension/toxaemia	4 (4%)	2 (2%)	43 (43%)	6 (22%)
Use of tocolytics	0	9 (9%)	19 (19%)	0
African descent	98 (100%)	100 (100%)	19 (19%)	25 (93%)
Twin pregnancy	6 (6%)	6 (6%)	13 (13%)	2 (7%)
Mortality	15 (15·3%)	15 (15%)	9 (9%)	11 (40·7%)

For Haiti, South Africa, and USA (2005), data are mean (SD, range) for age and mean (range) for gravidity. *Single centre prospective study. †Multicentre retrospective study, including survey questionnaire. ‡Single centre retrospective study. §Report included gravida 1–2 together as a group.

Table: Comparison of potential risk factors and mortality rates in PPCM

in different areas. However, cultural practices in some areas such as heavy intake of lake salt and body heating in clay beds, might precipitate pregnancy-associated heart failure that does not always fit the diagnostic criteria for PPCM.[16–20]

Although not clearly delineated, suggested risk factors associated with PPCM have included age, gravidity or parity, African origin, toxaemia or hypertension of pregnancy, use of tocolytics, and twin pregnancy. The incidence of these presumed risk factors reported in the three largest series of patients with PPCM[3,8,9,11,21] and in Demakis and colleague's[1,22] original report of the condition are shown in the table.

Although PPCM is thought to be more prevalent in the upper and lower extremes of childbearing age, and in older women of high parity,[12,23] it is important to note that 24–37% of cases may occur in young primigravid patients.[1,3,9,11,12,21,22] The largest prospectively-identified case series reports, from Haiti[11] and South Africa,[21] did not show a disproportionate role for older age, multiparity, and long-term use of tocolytic agents in the development

of PPCM. The association with race might be confounded by the observed increased frequency of PPCM in women of lower socioeconomic status.

Aetiology

The cause and mechanism of pathogenesis of PPCM remain unknown, and many hypotheses have been proposed (figure 1).[24–29] Early suggestions that nutritional disorders, such as deficiencies in selenium and other micronutrients, might contribute could not be confirmed in studies of Haitian patients with PPCM,[27] although unidentified nutritional factors might exist.

Because of immune-system changes related to pregnancy, associations with autoimmune mechanisms and inflammation have been studied since the 1970s. Melvin and colleagues[30] proposed myocarditis as the cause for PPCM and reported a dense lymphocyte infiltrate with variable amounts of myocyte oedema, necrosis, and fibrosis in right ventricular biopsy specimens. Treatment with prednisone and azathioprine resulted in clinical improvement and loss of inflammatory infiltrate on repeated biopsies in the three patients studied. Sanderson and colleagues,[31] and subsequently Midei and colleagues,[32] emphasised the association between myocarditis and development of PPCM. Although their findings were intriguing, they failed to establish a causal link. Additionally, Rizeq and colleagues[33] found an inflammatory component in less than 10% of biopsy samples from patients with PPCM, a proportion similar to that found in age-and-sex-matched patients with idiopathic dilated cardiomyopathy. A decade later, Felker and colleagues[34] confirmed that the absence or presence of inflammation on endomyocardial biopsy tissue did not predict outcome in patients with PPCM.

A viral trigger for the development of PPCM has been postulated and investigated in several studies. Bultmann and colleagues[35] identified viral genomic material in endomyocardial biopsy tissue from patients with PPCM; however, the same incidence and types of viral positivity were noted in controls. The findings of Kuhl and colleagues[25] in idiopathic dilated cardiomyopathy are
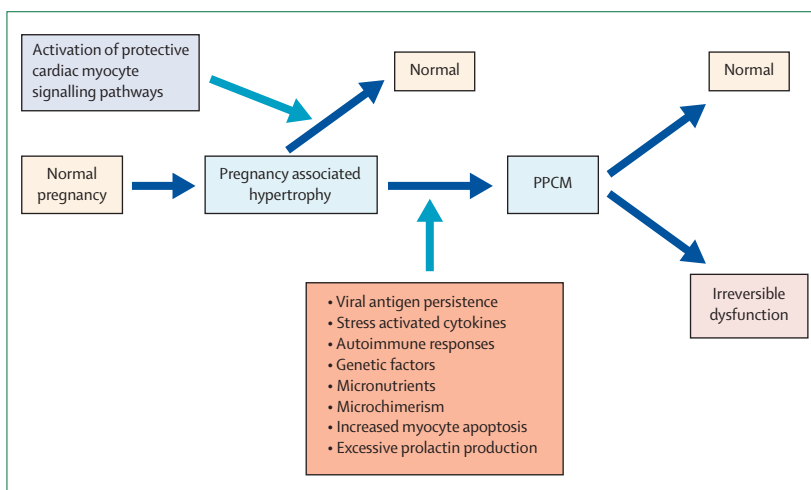

Figure 1: Proposed factors investigated contributing to the pathogenesis for PPCM
References for factors listed: protective signalling pathway,[24] viral antigen persistence,[25] stress-activated cytokines,[9,20] autoimmunity,[26] micronutrients,[27] microchimerism,[26] myocyte apoptosis,[9,21,28] prolactin.[24,29]

more convincing evidence for the role of virus as a trigger for cardiomyopathy. The investigators demonstrated the presence of viral genomic material in endomyocardial biopsy tissue, including enterovirus (coxsackievirus), parvovirus B19, adenovirus, and herpesvirus. They also showed that clinical improvement of left ventricular systolic function was associated with viral clearing. If future results show that viruses play a part in the development of PPCM (and some forms of idiopathic dilated cardiomyopathy), endomyocardial biopsy could become increasingly important in PPCM and unexplained cardiomyopathy, especially in patients who do not improve with conventional treatment in the early weeks after diagnosis.[36,37]

Ansari and colleagues[26] investigated the role of fetal microchimerism (fetal cells in maternal blood during and after pregnancy) in patients with PPCM. In a small sample of patients, the amount of male chromosomal DNA in maternal plasma was significantly greater in patients with PPCM than in control mothers without PPCM during the third trimester of pregnancy, at term, and in the first week postpartum. The lower concentrations of this foreign protein could possibly contribute to tolerance of the fetus, permitting successful completion of pregnancy; increased levels could theoretically lead to the initiation of autoimmune disease, including an autoimmune myocarditis.

Findings from South Africa[9,21] and Haiti[26,38] lend support to the hypothesis that immune activation contributes to the pathogenesis of PPCM. Sliwa and colleagues[9,21] identified increased concentrations in plasma of the inflammatory cytokine tumour necrosis factor α (TNFα), C-reactive protein, and a plasma marker of apoptosis, Fas/Apo-1, in a large population of newly diagnosed patients with PPCM. Baseline concentrations of C-reactive protein correlated positively with baseline left ventricular end-diastolic and end-systolic diameters and inversely with left ventricular ejection fraction. Concentrations of Fas/Apo-1 in plasma were significantly higher in patients with PPCM than in healthy controls, and were a predictor of mortality. Concentrations of C-reactive protein in plasma can vary substantially between different ethnic groups, and as much as 40% of this variation is genetically determined.[39] Hypothetically, an increase in the intensity of an inflammatory response could be one of the many factors contributing to development of PPCM. The importance of raised high-sensitivity C-reactive protein in plasma of patients with new and evolving PPCM[10,40] merits additional evaluation.

A high incidence of postpartum mortality in mice with a cardiac-tissue-specific signal transducer and activator of transcription 3 (STAT 3) knockout of has been reported.[24] Before death, female mutant mice presented with symptoms of heart failure, reduced cardiac function, and apoptosis. Data from this study suggested that the cardiac-myocyte-specific STAT3 pathway is necessary for protection of the heart from postpartum stress, and that
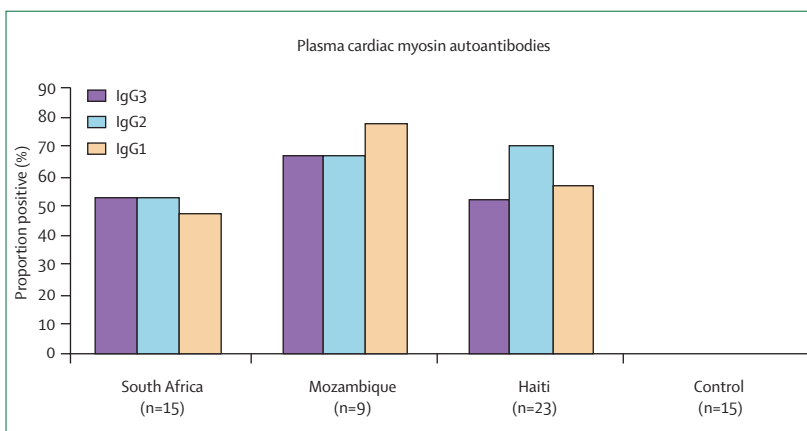

Figure 2: Comparison of immunoglobulin profiles in patients with PPCM from South Africa, Haiti, and Mozambique versus 15 healthy mothers from South Africa
Data from Warraich and colleagues.[38]

prolactin cleavage is crucially involved in the pathogenesis of PPCM. Additionally, data from another mouse model of PPCM suggest that apoptosis of cardiomyocytes has a causal role in PPCM, and that pharmacological inhibition of apoptosis by a caspase inhibitor might offer novel therapeutic strategies.[28] The finding of raised Fas/Apo-1 in women with PPCM[9] provides additional evidence for a role of apoptosis.

Warraich and colleagues[38] investigated the effect and clinical relevance of PPCM on humoral immunity and evaluated the immunoglobulins (class G and subclasses G1, G2, G3) against cardiac myosin in 47 patients with PPCM from South Africa, Mozambique, and Haiti. The immunoglobulin profiles were similar in the three regions and were markedly and non-selectively present (figure 2).

Although various causes for PPCM have been proposed, including abnormal hormonal regulation, the role of innate and adaptive immune systems, and the participation of autoantibodies, progenitor dendritic cells, T and B lymphocytes, cytokines, and chemokines,[29,38,41–48] so far no cause has been clearly identified. It is likely that the aetiology is multifactorial, and that the search for a cause is hampered by the rarity of this condition in the developed countries, where more research funds are available, by the lack of adherence to diagnostic guidelines, and by the heterogeneity of the populations studied.

Clinical presentation
The most common presentation of PPCM is with symptoms and signs of systolic heart failure.[1,8,9,12] Clinical examination of 97 patients seen in South Africa[12] over 4 years revealed a displaced hypodynamic apical impulse in 72% and gallop rhythm in 92% of the patients. Functional mitral regurgitation was present in 43%. Left ventricular hypertrophy by electrocardiographic voltage criteria was present in 66% and ST-T wave abnormalities in 96% of the patients. Additional symptoms and signs include

dependent oedema, dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, persistent cough, abdominal discomfort secondary to passive congestion of the liver and other organs, precordial pain, and palpitations. In the later stages postural hypotension may be prominent, reflecting low cardiac output and low blood pressure.

Early signs and symptoms of heart failure can be obscured by pregnancy, because often the patient considers them to be a normal part of pregnancy. New York Heart Association (NYHA) cardiac functional classification varies from NYHA I to IV, although most frequently initial presentation is with NYHA III and IV. Sudden cardiac arrest might occur in a situation where cardiopulmonary resuscitation is neither available nor successful.[49] Delayed diagnosis can be associated with increased morbidity and mortality. Clinicians should think of PPCM in any peripartum patient with unexplained disease. A broad index of suspicion is important, since unusual and non-heart failure presentations are also possible, as illustrated by the following evidence.

Left ventricular thrombus is common in PPCM patients with a left ventricular ejection fraction of less than 0·35.[9] With progression of disease, four-chamber dilation may be seen, with thrombus formation in the left atrium and right ventricle. Peripheral embolisation then becomes possible to any part of the body, including arterial occlusion of the lower extremities with compromised circulation,[8,50,51] cerebral embolism with hemiplegia, aphasia, and incoordination,[8,52] mesenteric artery occlusion with an acute abdomen syndrome secondary to bowel infarction,[8] and acute myocardial infarction secondary to coronary artery embolism.[53,54] Haemoptysis may be the presenting feature of co-existing pulmonary embolus, for which the patients also have an increased risk.[12]

A recent report[55] identified a 5-weeks postpartum 35-year-old mother who progressively deteriorated with acute hepatic failure and was being considered for liver transplant. An echocardiogram identified dilated cardiomyopathy as the reason for heart failure with subsequent passive congestion of the liver and severe hepatic failure. Appropriate treatment led to survival and recovery from liver failure as well as complete recovery of left ventricular systolic function.

Management and prognosis

The medical management of patients with PPCM is similar to that for other forms of heart failure, and has been reviewed in detail.[56] Treatment aims to reduce afterload and preload, and to increase contractility. Angiotensin-converting enzyme (ACE) inhibitors are usually used to reduce afterload by vasodilation if PPCM occurs after pregnancy. Because of potential toxic effects on the fetus, hydralazine (with or without nitrates) replaces ACE inhibitors during pregnancy. β blockers are used, since high heart rate, arhythmmias, and sudden death often occur in patients with PPCM. Digitalis, an inotropic agent, is also safe during pregnancy and may help to maximise contractility and rate control, but has to be closely monitored since excessive digoxin concentrations in serum have been associated with worse outcomes in women.[57,58] Women in general, and pregnant women in particular, may be more sensitive than men to its effect. Diuretics are also safe and are used to reduce preload and relieve symptoms. Because of the high incidence of thromboembolism in these patients, the use of heparin is also considered necessary, followed by warfarin in those with left ventricular ejection fractions of less than about 35%.

Although PPCM shares many features with other forms of non-ischaemic cardiomyopathy, an important distinction is that women with PPCM have a higher rate of spontaneous recovery of ventricular function. However, in a single centre prospective study of 100 South African patients with the condition, 15% died, and only 23% recovered normal left ventricular function after 6 months of treatment, despite optimal medical therapy with ACE inhibitors and β blockers.[21] In a longer follow-up study of prospectively identified patients in Haiti over 5 years, the mortality rate was also 15%, and 29 of 92 (31·5 %) recovered normal left ventricular function.[11] Continuing improvement was observed in the second and third years after diagnosis, confirming that the recovery phase is not limited to the first 6–12 months.

Subsequent monitoring depends on response to treatment, and includes a follow-up echocardiogram in the first several weeks to confirm improvement of left ventricular systolic function. After that, an echocardiogram is indicated about every 6 months until recovery is confirmed or a plateau is reached. The best time to discontinue ACE-inhibitors or β blockers is unknown; however, one or both of these medications should be continued for at least 1 year. Where resources exist, left ventricular assist devices and heart transplantation may be used if necessary.[59, 60]

Limited studies have been done with the use of immunosuppressive drugs such as azathioprine and steroids, and have shown mixed results. Use of these agents should be reserved pending further assessments, and perhaps should be restricted to patients with biopsy-proven lymphocytic myocarditis in the absence of viral particles. Recent studies in some patients with idiopathic dilated cardiomyopathy suggest a prominent role for cardiotrophic viruses.[25,37] As noted previously, only one investigation to date has identified viral genomic material in endomyocardial tissue from patients with PPCM.[35] Hence, PCR testing for a range of cardiomyotropic viruses could become important in the investigation of patients who do not improve in the early weeks following diagnosis.

Aside from their haemodynamic benefits, the angiotensin-converting enzyme inhibitors, β blockers, and angiotensin-receptor blockers may have an additional benefit to dampen an over-active immune system that plays a role in the basic pathophysiology of PPCM.[61–63]

Given the potential inflammatory nature of PPCM there may also be a role for other immunomodulatory therapy. A prospective study of 59 consecutive women with PPCM reported a significant reduction in the inflammatory marker TNFα and improved outcome in patients receiving the immunomodulating agent pentoxifylline in addition to conventional therapy.[64]

Long-term prognosis

Very few studies have been done to investigate the long-term survival and recovery outcomes in patients with PPCM. Felkner and colleagues[34] assessed the survival of patients with initially unexplained cardiomyopathy referred for endomyocardial biopsy Johns Hopkins hospital. Patients with PPCM seemed to have a better prognosis than those with other forms of cardiomyopathy. However, patients who died soon after diagnosis were probably not included in that study. Fett and co-workers,[11] with over 5 years of echocardiographic observations, noted continuing improvement in cardiac function well beyond the initial 6–12 months after diagnosis (figure 3).

Subsequent pregnancy and long term outcome

One of the greatest concerns of PPCM patients is the safety of additional pregnancies. Since many patients with PPCM develop the disease during or shortly after their first pregnancy, it is especially important to be able to provide them with information about relapse. In a retrospective study, Elkayam and colleagues[65] found that subsequent pregnancy in women with PPCM was associated with significant decrease in left ventricular function that resulted in clinical deterioration and even death. Symptoms of heart failure occurred in 21% of those who entered the subsequent pregnancy with normal left ventricular systolic function and 44% of those who entered the subsequent pregnancy with abnormal left ventricular systolic function. However, all deaths (three of 44, 7%) occurred in the group who entered the subsequent pregnancy with abnormal systolic function. Eventual recovery of left ventricular systolic function occurred more frequently in women who had an ejection fraction of greater than 30% at original diagnosis of PPCM.

Serial studies of left ventricular function and TNFα in prospectively-studied African patients with subsequent pregnancy after PPCM showed that deterioration of left ventricular function occurred postpartum to the subsequent pregnancy in five of six patients and was accompanied by raised concentrations of TNFα in plasma.[66]

In a study[67] of 15 prospectively-identified Haitian patients with a subsequent pregnancy after PPCM, seven patients tolerated the subsequent pregnancy without worsening heart failure whereas eight had a relapse. Of those who relapsed, only one regained normal left ventricular systolic function during the 2-year follow-up after the subsequent pregnancy. All those who did not relapse went on to recover normal left ventricular systolic
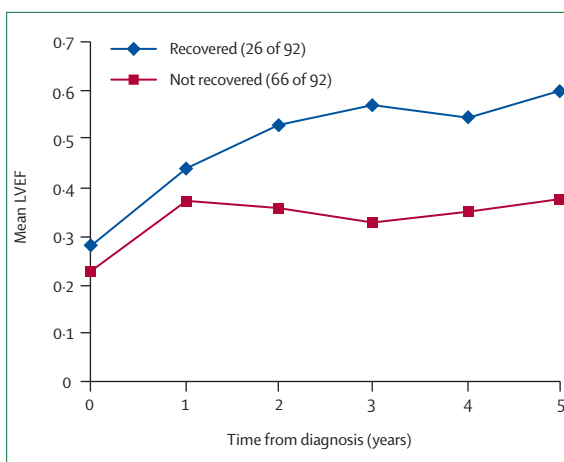

Figure 3: Echocardiographic data for left ventricular ejection fraction (LVEF) for 92 patients with peripartum cardiomyopathy followed up at Albert-Schweitzer Hospital, Haiti
From Fett and colleagues[11] with permission from *Mayo Clinic Proceedings*.

function. The longer follow-up allowed identification of both late recovery and late deterioration, again emphasising that recovery of heart function is not limited to the first 6–12 months after diagnosis or relapse.

Family-planning counselling is an important aspect of the care of patients after a diagnosis of PPCM. Subsequent pregnancy after a diagnosis of PPCM carries higher risk of relapse if left ventricular systolic function is not fully recovered first; and even with full recovery some additional risk of relapse remains.[65]

Implications for research

Reliable population-based information about incidence and prevalence of PPCM is essential to the development of national and international health policies for prevention and control of this condition. These should include a genetic epidemiological design to estimate the contribution of genetic susceptibility factors to this condition. While investigation continues on the molecular basis of PPCM, controlled trials are also needed for potential new treatments—including apheresis, immunoadsorption, immunosuppression, and antiviral agents—all of which might have a role, as suggested by initial reports from research in idiopathic dilated cardiomyopathy.[68–71] The promising results[64] that have been obtained with pentoxifylline in a non-randomised trial need to be tested in large multicentre randomised trials with the power to assess mortality and morbidity benefits.[72]

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