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Evolving management and improving outcomes of pregnancy-associated spontaneous coronary artery dissection (P-SCAD): a systematic review

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ABSTRACT

Background: Pregnancy-associated spontaneous coronary artery dissection (P-SCAD) is defined as SCAD occurring during pregnancy or within 3 months post-partum. Earlier systematic reviews have suggested a high maternal and foetal mortality rate. We undertook a structured systematic review of P-SCAD demographics, management and maternal and foetal outcomes.

Methods: Case study identification was conducted according to PRISMA guidelines, with screening of all published P-SCAD cases not meeting pre-defined exclusion criteria. Of two hundred and seventy-three publications screened, one hundred and thirty-eight cases met inclusion criteria. Cases were allocated to one of three time periods; 1960–85 (twenty cases) reflecting early management of P-SCAD, 1986–2005 (forty-two cases) reflecting recent management, and 2006–16 (seventy-six cases), reflecting contemporary management.

Results: The only significant demographic change in women experiencing P-SCAD over the last 50 years was an increasing proportion of primigravidas ($p = 0.02$). Management and outcomes, however, have altered significantly. Emergent angiography ($p < 0.0001$), reduced thrombolysis ($p = 0.006$) and increasingly conservative or percutaneous management ($p < 0.0001$) are associated with dramatic reductions in maternal mortality (85% in earliest reports to 4% in the last decade, $p < 0.0001$) and foetal mortality (50% in earliest reports to 0.0% in the last decade, $p = 0.023$).

Conclusion: This systematic review of temporal changes in presentation, management and outcomes of P-SCAD represents the widest range of variables analysed in the largest cohort of P-SCAD patients to date. In the setting of earlier coronary angiography and increasingly conservative management, maternal and foetal survival rates continue to improve.

1. Case study

A 35-year-old G2P0 woman presented with chest pain and anterior ST elevation at ± 34 weeks and 3 days gestation of an in vitro fertilisation (IVF) pregnancy. She had undergone two cycles of IVF therapy prior to pregnancy, and received a standard regime of hormonal stimulation. After discussion with the treating obstetrician, the cardiac catheterization laboratory was activated, with midwives and an obstetrics registrar on standby for urgent delivery in case of foetal distress or maternal arrest.

Radial coronary angiography performed with minimal contrast (70 mL), minimal radiation (skin dose 88 mGy), and abdominal shielding. A spontaneous dissection of our patient's distal left anterior descending artery was found. Due to her haemodynamic stability, the decision was made to treat her conservatively with optimal medical therapy.

Our patient commenced aspirin, clopidogrel, metoprolol and a heparin infusion (subsequently changed over to enoxaparin). Her electrocardiogram evolved to show anterior Q waves, and troponin peaked at 40,494 ng/L (normal < 16 ng/L). Echocardiography showed anterior hypokinesis with an ejection fraction (LVEF) of 40%, and spontaneous echocontrast in the left ventricle. Screening for an underlying connective tissue disease, including a full vasculitic screen and imaging of cerebral and renal vasculature, was negative. She remained on cardiac monitoring, and daily foetal cardiotocography remained within normal limits.

At 38 weeks exactly gestation, our patient underwent elective lower uterine segment caesarean section under spinal anaesthesia, with clopidogrel cessation one week prior and enoxaparin cessation 48 h prior. Delivery was uncomplicated, with birth of a healthy female singleton. Post-partum, our patient commenced ramipril and warfarin, with agreement not to breastfeed. Seven days later, our patient returned home with her daughter, stable with New York Heart Association class I symptoms.

2. Methods

We conducted a systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [1], examining all case studies and case series published on pregnancy-

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associated spontaneous coronary artery dissection (P-SCAD) at any time up to December 2016. Two authors (EP and CK) searched on PubMed and EMBASE using the search term 'pregnancy AND spontaneous coronary artery dissection'. Prior published case reviews were identified, and cases cross-referenced with our search results. Citation tracking and searches of major journal databases were also performed to maximise case identification.

In line with accepted clinical definitions, P-SCAD was defined as spontaneous coronary artery dissection occurring during pregnancy or within 3 months post-partum [2]. The definition of pregnancy did not include patients undergoing IVF therapy not yet confirmed to be pregnant or receiving b-HCG injections for weight-loss purposes [3,4]. The diagnosis of P-SCAD was required to be confirmed either by invasive coronary angiography or at autopsy. Combined exclusion criteria included articles not in English, narrative reviews, healthcare system linkage studies without individual case details, cases not meeting pre-defined P-SCAD criteria, diagnosis made by cardiac imaging (i.e., CT coronary angiography only performed), full article not able to be accessed, or histopathology articles reporting autopsy findings of P-SCAD with minimal clinical history.

Our search strategy returned 273 results. Exclusion of duplicate results and articles not meeting specified a priori criteria (162 articles) resulted in 111 articles describing 138 cases of P-SCAD [5–92].

Demographic case details extracted from all case reports were maternal age, cardiac risk factors (defined as both number of cardiac risk factors and a binary variable), presence of an autoimmune or connective tissue disorder, gravidity/parity status, gestational time or days post-partum at onset of P-SCAD, and whether the pregnancy was a result of in vitro fertilisation (IVF) or a multiple pregnancy.

Parameters assessed with regards to cardiac presentation and outcome included mode of cardiac presentation (defined as ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, unstable angina or out of hospital cardiac arrest), culprit coronary artery and whether multivessel dissection was present, whether thrombolysis was used, whether the patient was taken emergently for coronary angiography, whether mechanical cardiac support such as an intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) was employed, treatment strategy (defined as conservative medical management, percutaneous coronary intervention, coronary artery bypass surgery or death prior to definitive coronary intervention), whether the patient subsequently underwent cardiac transplant, and mean left ventricular ejection fraction at follow-up.

With regards to obstetric management and outcome, we assessed whether emergency delivery was required if pregnant at time of P-SCAD, mode of delivery chosen (defined as normal vaginal birth or lower uterine segment caesarean section), and maternal and foetal survival rates.

2.1. Statistical analysis

Cases were grouped into three cohorts according to year of publication. The three categories reflected early management of P-SCAD in the years 1960–85 (twenty cases), management over the interval twenty years from 1986 to 2005 (forty-two cases) and contemporary management in the last decade (2006–16, seventy-six cases published).

A Shapiro-Wilk test was used to assess normality of distribution of continuous variables. Continuous variables that were normally distributed were assessed with a one-way ANOVA test with post-hoc Tukey testing, and are presented as mean ± standard deviation. Continuous variables that were not normally distributed were assessed with Kruskal-Wallis testing and are presented as median values with interquartile ranges. Categorical variables are reported as proportions, and were assessed with chi-squared testing. All statistical calculations were performed using STATA software (StataCorp 2015, Texas).

3. Results

Mean maternal age did not differ across time cohorts; however, there were significant differences regarding gravidity/parity status at each time point (Table 1). In all time cohorts, the majority of patients were post-partum, with a median post-partum status of approximately two weeks. Patients in all cohorts had a mean age in the mid-thirties, however patients in the 1960–85 cohort had a median of three children at this age, compared to a median of 1 child for women in the 1986–2005 cohort, and 2 children in the 2006–16 cohort ($p = 0.001$). This was also reflected in a difference in the proportion of primigravidas across groups: the proportion of primigravidas peaked in the time period 1986–2005, representing over half of women experiencing P-SCAD ($p = 0.03$). As reported in earlier studies, P-SCAD most commonly occurred in the third trimester or postpartum period (105). Amongst women experiencing post-partum P-SCAD, dissection occurred progressively closer to the time of delivery in recent cohorts (11.5 days PP in 2006–16 vs 13.0 (1986–2005) vs 20.5 days (1960–1985), $p = 0.046$).

IVF-assisted pregnancies complicated by P-SCAD were only reported for the first time in the most recent decade 2006–16. However, due to small overall numbers, the difference between groups with regards to IVF therapy did not reach statistical significance. Likewise, multiple pregnancies were increasingly common in the most recent cohort, however the difference did not reach statistical significance. Due to the small numbers, assessment of statistical interaction between IVF status and multiple pregnancies was not feasible.

Multiple therapeutic strategies differed significantly between groups over time (Table 2). Women experiencing P-SCAD in the last decade have been significantly less likely to present with out of hospital cardiac arrest or receive thrombolysis ($p < 0.0001$ and $p = 0.006$ respectively). They were significantly more likely to receive urgent coronary angiography ($p < 0.0001$), and conservative management or percutaneous coronary intervention than coronary artery bypass surgery ($p < 0.0001$).

With regards to outcome measures, maternal and foetal survival have both increased dramatically from earliest reports to the current decade (15 to 96%, $p < 0.0001$ and 50 to 100%, $p = 0.023$ respectively), and women are less likely to require cardiac transplantation for cardiomyopathy ($p = 0.008$). However, there have been no significant changes in mean ejection fraction at follow-up. Follow-up time period were very inconsistently documented amongst studies, or not reported at all. Consequently, length of follow-up has not been included in our data-set.

4. Discussion

P-SCAD is a high-risk condition, with the potential for dual mortality [87]. It occurs in approximately 1.81 per 100,000 pregnancies [88].

Table 1
Baseline demographics of women experiencing P-SCAD.

	2006–16	1986–2005	1960–85	Significance
Number of case reports	76	42	20	–
Maternal age (years)	34.1 ± 4.9	32.9 ± 5.0	34.8 ± 5.1	P = NS
Primigravida status (%)	32.3	54.8	14.3	**$P = 0.02$**
Median gravidity	2 [2–3]	2 [1–3]	3 [2–4]	P = NS
Median parity	2 [1–2]	1 [1–2]	3 [2–4]	**$P = 0.001$**
IVF pregnancy (%)	5.3	0.0	0.0	P = NS
Multiple pregnancy (%)	9.2	2.4	5.0	P = NS
Cardiac risk factors present (%)	45.1	31.0	30.0	P = NS
Median number of cardiac risk factors	0 [0–1]	0 [0–1]	0 [0–1]	P = NS
Autoimmune disease (%)	7.0	4.9	5.0	P = NS
Pregnant (%)	23.7	33.3	10.0	P = NS
Median gestational week[a]	34 [32–36]	33.5 [23–37]	40 [40–40]	P = NS
Postpartum (%)	76.3	66.7	90.0	P = NS
Median postpartum days[b]	11.5 [7–21]	13 [5–42]	20.5 [14–42]	**$P = 0.046$**

IVF = in vitro fertilisation.
[a] If pregnant.
[b] If postpartum.

Table 2
Management strategies and cardiac and obstetric outcomes.

	2006–16	1986–2005	1960–86	Significance
Cardiac presentation	UA 0.0% NSTEMI 39.5% STEMI 60.5% OOHCA 0.0%	UA 4.8% NSTEMI 14.2% STEMI 76.2% OOHCA 4.8%	UA 5.0% NSTEMI 10.0% STEMI 15.0% OOHCA 80.0%	***P* < 0.0001**
Multivessel dissection (%)	44.7	23.8	30.0	*P* = NS
Thrombolysis (%)	2.6	16.7	0.0	***P* = 0.006**
Urgent angiography (%)	80.2	35.7	0.0	***P* < 0.0001**
IABP or ECMO (%)	21.1	21.4	5.0	*P* = NS
In-hospital cardiac arrest (%)	11.8	22.0	15.0	*P* = NS
Cardiac treatment strategy	CM 28.9% PCI 38.2% CAGS 32.9%	CM 41.5% PCI 22.0% CAGS 34.1% DBI 2.4%	CM 10% PCI 0.0% CAGS 5.0% DBI 85.0%	***P* < 0.0001**
Urgent delivery required (%)[a]	50.0	57.1	50.0	*P* = NS
Mode of delivery[a]	CS 100%	CS 71.4% NVB 7.1% IUD 21.4%	CS 50% IUD 50%	*P* = NS
Maternal survival (%)	96.0	92.9	15.0	***P* < 0.0001**
Foetal survival (%)[a]	100.0	71.4	50.0	***P* = 0.023**
Mean EF at follow-up (%)	45.3 ± 12.5	45.3 ± 15.7	54.0[b]	*P* = NS
Cardiac transplant	0.0	9.8	0.0	***P* = 0.008**

CAGS = coronary artery graft surgery; CM = conservative management; CS = Caesarean section; DBI = death before intervention; ECMO = extra-corporeal membrane oxygenation; EF = ejection fraction; IABP = intra-aortic balloon pump; IUD = in utero death; NSTEMI = non-ST segment elevation myocardial infarction; NVB = normal vaginal birth; OOHCA = out of hospital cardiac arrest; PCI = percutaneous coronary intervention; STEMI = ST-segment myocardial infarction; UA = unstable angina.

[a] If P-SCAD occurred while pregnant rather than postpartum.

[b] Only one ejection fraction reported in this dataset.

Multiple previous reviews have been published on the topic of P-SCAD (Table 3), with varying degrees of patient inclusion and clinical findings [43,89–92].

Our review is the largest to date, and includes variables not previously reported upon, including use of IVF therapy, primigravida status, presence of autoimmune disease, presence of cardiac arrest, use of advanced mechanical therapies such as IABP or ECMO, whether urgent delivery was required, and foetal survival. By classifying all cases into one of three temporal groups, we have sought to objectively assess trends in patient demographics, management and maternal foetal outcomes for the first time.

4.1. Demographics

In the last decade, there has been an increasing prevalence of a history of IVF in pregnancies complicated by P-SCAD, although numbers were too small to identify statistical significance between groups. Of seventy-six patients with P-SCAD reported in the last decade, four (5.3%) had used IVF to enable conception, compared to zero in all prior decades. A further fifth case study [3] described a woman undergoing IVF therapy who suffered SCAD; this case was excluded from analysis due to pregnancy not being confirmed. Details are not available in all cases regarding number of cycles of IVF undergone prior to pregnancy, or exact mode of embryonic transfer; however, these would be enlightening to document in future cases.

Several reasons may underlie the increasing prevalence of IVF-associated P-SCAD. Firstly, although mean maternal age was not statistically different between groups, the proportion of primigravidas is increasing with time. Interestingly, the proportion of primigravidas was actually highest in the time period 1986–2005. The increased hormonal exposure associated with IVF has been hypothesised to contribute to an elevated risk of spontaneous vascular dissection [93], although currently this remains speculative. Alternatively, the increasing prevalence of IVF in P-SCAD pregnancies may simply reflect the increasing societal prevalence of IVF. Over the last decade, IVF has been used to assist pregnancy in up to 3.5% of Australian pregnancies [94,95]; this societal prevalence is broadly equivalent to the prevalence in our study.

4.2. Management and outcomes

Over the last sixty years, there have been significant changes in the management of acute coronary syndrome. The earliest reports of P-SCAD were of a universally fatal condition presenting with out of hospital cardiac arrest, and the first survival from P-SCAD was not reported until 1975 [96]. In the majority of case reports, a history of chest pain in the days prior to cardiac arrest was retrospectively obtained from relatives. Improved recognition of cardiac symptoms and development of pre-hospital management protocols for chest pain assessment may have contributed to the reduced pre-hospital mortality currently observed from P-SCAD.

Within improved protocols for chest pain assessment and diagnosis, early coronary angiography for high-risk chest pain is increasingly emphasised [97]. Rates of emergent coronary angiography in reported cases of P-SCAD have significantly increased across the documented time periods. Of note, this increase in rates of emergent coronary angiography does not necessarily correlate with increased coronary intervention. In the last decade, rates of conservative management have been roughly equivalent to rates of percutaneous coronary intervention and cardiac surgery. The use of mechanical cardiac device therapy such as IABPs has also not significantly increased over time.

It would appear that although rates of coronary intervention and mechanical cardiac support have not significantly increased over time, an approach emphasizing emergent diagnostic angiography is associated with improved mortality. Early diagnostic angiography facilitates definition of the patient's coronary anatomy, with subsequent appropriate risk-stratification and management decision. The choice of management approach should then incorporate both knowledge of the coronary anatomy and appreciation of the patient's clinical status [98]. In their review, Vijayaraghavan recommend optimal medical therapy for all P-SCAD patients in the first instance unless there is left main dissection, ongoing chest pain, electrocardiographic evidence of ischaemia, ventricular arrhythmias or haemodynamic instability. In these patients, PCI should be performed where feasible, with CABGs reserved for patients with left main or multi-vessel dissection [99]. We suggest (Table 4) a standardized approach to assessment and emergent management of P-SCAD patients in the cardiac catheterization laboratory, based upon our review of the literature and personal clinical experience [55,82,86].

One of the major factors likely to have also contributed to improved maternal and foetal cardiac outcomes over sixty years is improvement in medical therapy. The last sixty years have witnessed the introduction of medications such as ACE inhibitors and beta blockers, with consequent dramatic reduction in mortality from acute coronary syndromes. Due to incomplete documentation of patients' medical therapy, we were not able to include full medical regimens in the analysis. However, it is presumed that contemporary optimal medical therapy was prescribed to each patient, within the limitations of any contraindications from their pregnancy (for example, ACE inhibitors are contraindicated in pregnancy and the first month of breastfeeding).

Thrombolysis is the one medical strategy that was routinely captured in our dataset, with significant differences observed between time periods. Thrombolysis was not used in any published case reports of P-SCAD prior to 1986. The GISSI-1 trial published in 1986 [100] was the first major trial to demonstrate a mortality benefit from the use of thrombolysis in STEMI; subsequent to this trial, thrombolysis was utilized in one in six cases of P-SCAD from 1986 to 2005. However, thrombolysis in pregnancy does not have high-level supportive evidence, and rates of thrombolysis in P-SCAD have

Table 3
Findings of prior reviews of management and outcomes of P-SCAD.

Review	Year of publication	Time period included	Number of patients included	Parameters assessed	Findings
Koul et al	2001	1952–99	58	• Age • Parity • Cardiac risk factors • Presentation • Thrombolysis • Culprit vessel • Cardiac management strategy • Maternal survival	• 62% maternal survival rate • 77.6% of cases post-partum
Maeder et al	2005	1952–2004	16[a]	• Age • Parity • Cardiac risk factors • Presentation • Culprit vessel • Cardiac management strategy • Results of follow-up angiography	• 31% of patients who received conservative therapy strategy had completely resolved dissections at follow-up angiography
Appleby et al	2009	1999–2008	25	• Age • Parity • Cardiac risk factors • Event time • Culprit vessel • Cardiac management strategy • Maternal survival	• 100% maternal survival rate
Sheikh et al	2012	1952–2009	118	• Age • Parity • Cardiac risk factors • Event time • Culprit vessel • Cardiac management strategy	• Reported 50% maternal mortality at presentation
Higgins et al	2013	1998–2009	47	• Age • Event time • Cardiac risk factors • Presentation • Culprit vessel • Cardiac management strategy	• 100% maternal survival • 6% foetal mortality • 6% cardiac transplant

[a] This review required patients to have had a follow-up coronary angiogram, thus excluded 70/86 cases identified in literature.

subsequently declined. In the last decade, just one in thirty-eight cases of P-SCAD received thrombolysis; as mentioned earlier, this may correspond with a significant shift towards earlier diagnostic coronary angiography.

Interestingly, despite improvements in medical therapy, mean ejection fraction at follow-up has not significantly improved amongst maternal survivors of P-SCAD. However, 'follow-up' has not been defined as a consistent routine time point amongst publications. There may also be a survival bias in that patients who would previously have died at the index event now survive, but with lower ejection fractions, reducing the overall mean.

4.3. Study limitations

There are multiple limitations to our review. Firstly, it is by nature retrospective, and thus dependent on details recorded for accurate data capture. Our data set is also by definition vulnerable to publication bias, as this reflects a series of P-SCAD cases deemed novel enough for publication. Consequently, management and outcomes may differ slightly to outcomes that would be observed in an unselected registry of P-SCAD patients. However, in the absence of any prospective trials or registries, our review comprises the largest review of P-SCAD management and outcomes to date. We believe the temporal trends demonstrating improved maternal and foetal outcomes are reassuring, and will enable clinicians to provide contemporary data and prognostication to their patients experiencing P-SCAD.

5. Conclusion

Although previous reviews have been published on the topic of P-SCAD, ours is the first to compare changes in presentation, management and outcome over the decades. Our review suggests that there have been significant changes in management of P-SCAD, with reduced thrombolysis and a shift to emergent diagnostic coronary

Table 4
Recommendations for management of P-SCAD patients in the cardiac catheterization laboratory.

1. Patients with STEMI on their presenting ECG should have urgent coronary angiography to define coronary anatomy.
2. Patients without STEMI on their presenting ECG but with significant troponin rise or ongoing chest pain should be considered for early coronary angiography to define coronary anatomy.
3. Thrombolysis should be avoided in cases of pregnant patients with STEMI and urgent angiography facilitated.
4. During angiography, the patient's right hip should be supported (i.e., with a wedge or pillow) so that the patient is tilted to the left. This reduces the risk of IVC compression and consequent reduction in cardiac preload.
5. Radial access should be first-line choice of access, to minimise direct screening of the abdomen with radiation.
6. The abdomen should be shielded with lead throughout the case.
7. Radiographers should ensure that radiation delivery, field size and frame rate are all optimised to ensure minimum radiation (while ensuring interpretable pictures).
8. Obstetric monitoring facilities (i.e. CTG) should be brought to the catheterization laboratory to provide appropriate foetal monitoring throughout the case
9. An obstetrician and peri-mortem Caesarean section equipment should be available throughout the case, if gestational age is >24 weeks. In case of maternal cardiac arrest, the baby should be delivered within 5 min of arrest, while maternal resuscitation efforts continue.
10. P-SCAD should be managed conservatively with optimal medical therapy unless the patient has left main dissection, is haemodynamically unstable or experiencing refractory arrhythmias.

CTG = cardiotocography; ECG = electrocardiogram; IVC = inferior vena cava; STEMI = ST elevation myocardial infarction.

angiography. Outcomes have markedly improved, with mortality in the last decade reduced to <5% for both mother and baby.

CAGS = coronary artery graft surgery; CM = conservative management; CS = Caesarean section; DBI = death before intervention; ECMO = extra-corporeal membrane oxygenation; EF = ejection fraction; IABP = intra-aortic balloon pump; IUD = in utero death; NSTEMI = non-ST segment elevation myocardial infarction; NVB = normal vaginal birth; OOHCA = out of hospital cardiac arrest; PCI = percutaneous coronary intervention; STEMI = ST-segment myocardial infarction; UA = unstable angina.

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