

Cardiovascular and pregnancy outcomes in women with coronary microvascular dysfunction: a case series

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Background

Coronary microvascular dysfunction (CMD) is associated with adverse cardiovascular outcomes. Coronary microvascular dysfunction is observed in women of childbearing age, however, the frequency of adverse pregnancy outcomes (APO) is unknown.

Case summary

Women previously enrolled in a single centre prospective CMD registry diagnosed using invasive coronary reactivity testing were included. Among 279 women enrolled, 5 of 47 (10.6%) of childbearing age (18–44 years) subsequently became pregnant, representing a fertility rate of 36.8 births per 1000 women-years. None had history of hypertension, diabetes, or smoking. Four (80%) had a history of prior spontaneous miscarriage. Median age at CMD diagnosis was 32 years (IQR: 32–35). During pregnancy, most reported stable or improved angina, while one reported increased angina frequency, an emergency room visit and accelerated anti-anginal therapy. None experienced gestational hypertension, diabetes, pre-eclampsia, myocardial infarction, or death. Two (40%) experienced APO of preterm delivery and small neonate for gestational age. Following pregnancy, angina severity scores, and/or functional capacity decreased in three women (60%).

Discussion

In this first case-series of five women with CMD who became pregnant, increased angina and accelerated care during pregnancy and post-partum was not commonly observed. Fertility rates were lower than the national average, while prior spontaneous miscarriage and subsequent APO were higher. Further studies are warranted to understand and manage pregnancy in women with CMD, as well as the impact of pregnancy on longer term angina, functional capacity, and outcomes.

Keywords

Coronary microvascular dysfunction • Pregnancy • Outcomes • Case series

Learning points

- A relatively high rate of 40% adverse pregnancy outcomes (APO) was observed; increased angina and accelerated care during pregnancy and post-partum was not common at 20%.
- We hypothesize that APO may be due to an interplay between coronary microvascular dysfunction, inflammatory conditions, and parallel anomalies in the uterine microvasculature; larger studies are needed to further explore these findings.

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Introduction

Coronary microvascular dysfunction (CMD) is a condition characterized by angina, evidence of ischaemia on non-invasive stress testing, the absence of obstructive coronary artery disease (CAD) and is more commonly observed in women. Coronary microvascular dysfunction is diagnosed by invasive coronary reactivity testing, including assessment of endothelial-dependent and independent function, and is associated with recurrent angina, angina hospitalizations, and adverse cardiovascular outcomes including myocardial infarction and cardiovascular mortality.¹

Although most CMD is diagnosed after menopause, up to 20% of women are pre-menopausal,² and potentially of childbearing age. Obstructive CAD is associated with significant maternal and foetal morbidity and mortality,³ and previous reports have shown an association between endothelial vascular dysfunction and complications of pregnancy.⁴ Maternal cardiac and pregnancy events in women with CMD has not been previously reported, limiting pregnancy counselling currently offered to these patients.

In this case series, we report cardiovascular and pregnancy outcomes of five women who became pregnant following a diagnosis of CMD.

Timeline

Case 1

2008/11	Initial reason for consultation—angina, history of SLE and rheumatoid arthritis
2008/11	Non-invasive testing—Stress CMRI showing stress-induced infero-lateral wall hypokinesis
2008/12	Coronary reactivity testing for definitive diagnostic testing
2009/11	Confirmation of pregnancy, unplanned—on ethinylestradiol/norethisterone acetate, epratuzumab, hydrochloroquine, prednisone, azathioprine, ramipril, carvedilol, and atorvastatin, which were all stopped once pregnancy was confirmed
2010/04	Lupus flare-up, hospitalization at 28 4/7 weeks, treated with prednisone
2010/07	Delivery at 37 4/7 weeks' gestation
2010/08	No adverse events reported at 6 weeks post-partum

Case 2

2009/04	Initial reason for consultation—angina, history of SLE
2009/12	Non-invasive testing—stress CMRI showing circumferential stress-induced hypoperfusion
2010/01	Coronary reactivity testing for definitive diagnostic testing
2012/08	Beta-blocker and statin stopped in anticipation of conception
2013/02	Cardiology follow-up—10 weeks pregnant, planned, not on contraception

2013/08	Delivery at 35 1/7 weeks' gestation
2013/09	No adverse events reported at 6 weeks post-partum
Case 3	
2010/02	Initial reason for consultation—angina
2010/02	Non-invasive testing—exercise cardiac SPECT—1.65 mm ST segment depressions on exercise ECG
2010/03	Coronary reactivity testing for definitive diagnostic testing
2010/09	Beta-blockers stopped in anticipation of conception
2011/08	Anaesthesiology consultation at 37 weeks' gestation, not on any medications
2011/09	Delivery at 40 6/7 weeks' gestation
2011/10	No adverse events reported at 6 weeks post-partum
Case 4	
2012/10	Initial reason for consultation—angina
2012/10	Non-invasive testing—exercise cardiac SPECT—12% reversible defect in mid-distal anterior wall
2012/11	Coronary reactivity testing for definitive diagnostic testing
2013/10	Carvedilol was switched to labetalol, and ranolazine stopped in anticipation of conception
2014/01	Transvaginal US confirming pregnancy at 13 weeks' gestation
2014/07	Cardiology follow-up—37 weeks' gestation, labetalol stopped given symptom improvement
2014/08	Delivery at 39 5/7 weeks' gestation
2014/09	No adverse events reported at 6 weeks post-partum
Case 5	
2014/10	Initial reason for consultation—angina
2014/10	Non-invasive testing—stress CMRI showing circumferential stress-induced hypoperfusion
2014/11	Coronary reactivity testing for definitive diagnostic testing
2014/12	Labetalol started in anticipation of conception
2016/12	ER visit for chest pain at 7 weeks gestation by LMP
2017/01	Transvaginal US confirming pregnancy at 11 weeks' gestation
2017/02	Cardiology follow-up—labetalol increased to 100 mg PO TID
2017/04	Cardiology follow-up—symptoms improved on labetalol 100 mg TID
2017/08	Delivery at 40 0/7 weeks' gestation
2017/09	No adverse events reported at 6 weeks post-partum

CMRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; SLE, systemic lupus erythematosus; SPECT, single photon emission computed tomography.

Methods

Women previously enrolled in a tertiary academic centre prospective CMD registry were screened for pregnancy following enrolment, through telephone interviews and chart review. Clinical characteristics and obstetrical history were collected at enrolment. Symptom frequency was assessed at baseline and annually using the Seattle Angina Questionnaire (SAQ), a validated self-administered 19-item

questionnaire sensitive to clinical changes in stable CAD patients.⁵ Baseline and yearly follow-up functional capacity in metabolic equivalents (METs) was estimated using the Duke Activity Status Index (DASI), a validated 12-item self-administered questionnaire,⁶ or estimated from medical records/SAQ questionnaire if DASI questionnaires were incomplete/unavailable. Coronary microvascular dysfunction was diagnosed by coronary reactivity testing following a previously published protocol.⁷ In the absence of obstructive CAD, a Doppler flow wire was placed into the left anterior descending artery to measure blood flow velocities.⁷ Coronary microvascular dysfunction was defined as abnormalities in ≥ 1 of four coronary microvascular function pathways: endothelial-independent pathways were tested by evaluating coronary flow reserve (CFR) in response to intracoronary (IC) adenosine [Normal ($N \geq 2.5$)] and change in coronary artery diameter in response to IC nitroglycerine [ΔNTG] ($N \geq 20\%$). Endothelial-dependent pathways were tested by evaluating increase in coronary blood flow [ΔCBF] to IC acetylcholine (Ach) ($N \geq 50\%$), and increase in coronary artery diameter in response to IC Ach [ΔACH] ($N > 0\%$).

Outcomes of interest were collected from the time of confirmation of pregnancy to 6 weeks post-partum and included self-reported increase in angina, emergency department visits or hospitalization for angina, myocardial infarction, or death. Adverse pregnancy outcomes (APO) included gestational hypertension, gestational diabetes, pre-eclampsia/eclampsia, preterm birth (<37 weeks, either spontaneous or medically indicated), and small for gestational age birthweight (<10th percentile for gestational age). Seattle Angina Questionnaire scores and DASI-estimated functional capacity at baseline, during pregnancy (when available), and at last available follow-up after pregnancy were collected. Fertility rate per 1000 women-years was calculated by dividing the number of births by the number of women-years for women of childbearing age (aged 18–44 years),⁸ multiplied by 1000.

Results

Among the prospective CMD registry of 279 patients with suspected CMD undergoing coronary reactivity testing, 54 (19.3%) were women were of childbearing age. Of these, 7 were lost to follow-up and information concerning pregnancies following enrolment was available in 47. Five women (10.6%) became pregnant following CMD diagnosis (Figure 1) during 135.6 women-years of follow-up,

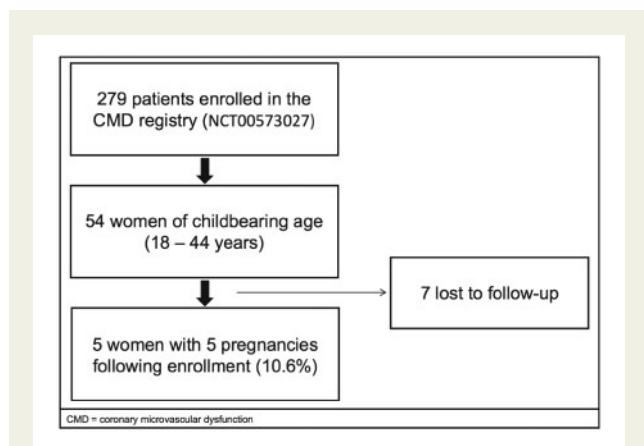


Figure 1 Flow-chart of women with coronary microvascular dysfunction who became pregnant following enrolment.

representing a fertility rate of 36.8 births per 1000 women-years. Clinical, pregnancy details, and CMD results are summarized in Tables 1 and 2. Baseline and follow-up SAQ scores and DASI-estimated functional capacity are summarized in Tables 3 and 4. None of the women had a history of hypertension, dyslipidaemia, diabetes mellitus, smoking, gestational diabetes, gestational hypertension, or pre-eclampsia. Four (80%) had a history of spontaneous miscarriage. Median age at diagnosis of CMD was 32 years [inter-quartile range (IQR): 32–35] and median age at pregnancy was 35 years (IQR: 34–36). Coronary reactivity testing demonstrated a median CFR of 2.3 (IQR: 2.1–2.6), median ΔNTG 17% (IQR: 12–21%), median ΔACH 11% (IQR: 0–11%), and ΔCBF 40% (IQR: 10–58%). Women were counselled on potential teratogenicity of angiotensin enzyme converting-inhibitors (ACEI), angiotensin receptor blockers (ARB), ranolazine and statins, frequently used to treat CMD. These agents were stopped prior to conception once women expressed intention to become pregnant. All women were advised to continue oral aspirin 81 mg once daily during pregnancy.

Case 1

This 32-year-old G4P3A1 (three previous uncomplicated pregnancies delivered at term and one spontaneous miscarriage) presented with angina. She had a past medical history of rheumatoid arthritis and systemic lupus erythematosus (SLE), treated with azathioprine 50 mg PO TID, plaquenil 200 mg PO BID and prednisone. On physical examination, vital signs were within normal range. Cardio-pulmonary auscultation and peripheral pulses were normal with no signs of volume overload. Coronary microvascular dysfunction diagnosed by CRT with two of four abnormal pathways (Table 1). She underwent stress cardiac magnetic resonance imaging (CMRI) which showed stress-induced infero-lateral wall hypokinesia. She had an unplanned pregnancy approximately 1 year after diagnosis. Systemic lupus erythematosus treatment was stopped upon confirmation of pregnancy and prednisone was restarted at 28 weeks' given suspicion of SLE flare-up. Carvedilol was stopped at the beginning of pregnancy. Self-reported frequency of angina was stable throughout pregnancy, which was free of adverse cardiac outcomes. She experienced an APO, as her female child was small for gestational age, weighing 2265 g at 37 weeks' gestation. Seattle Angina Questionnaire scores worsened and functional capacity remained stable at approximately 1-year follow-up (Tables 3 and 4).

Case 2

This 32-year-old G3P2A1 (two uncomplicated pregnancies delivered at term and one spontaneous miscarriage) woman with a history of SLE treated with plaquenil 400 mg PO daily and prior stroke initially presented with angina. On physical examination, vital signs were within normal range. Cardio-pulmonary auscultation and peripheral pulses were normal with no signs of volume overload. She underwent stress CMRI which showed circumferential stress-induced hypoperfusion. Coronary microvascular dysfunction was evident with two of four abnormal pathways (Table 1). Carvedilol was stopped prior to conception. Plaquenil was continued during pregnancy. She became pregnant 3 years after the CMD diagnosis. Self-reported frequency of angina remained stable throughout her pregnancy. She experienced medically indicated preterm delivery due to

Table 1 Clinical data and coronary reactivity testing results

Case	Age at CMD diagnosis (years)	Coronary reactivity testing findings				
		LVEDP (mmHg)	CFR	ΔNTG (%)	ΔCBF (%)	ΔACH (%)
1	32	10	1.6	31	40	11
2	32	11	2.3	17	58	11
3	35	12	2.1	21	89	17
4	35	17	3.3	12	10	-8
5	26	10	2.6	10	-8	0

Abnormal values are in bold.

CMD, coronary microvascular dysfunction; CFR, coronary flow reserve; normal (N) ≥ 2.5 ; Δ CBF, change in coronary blood flow in response to acetylcholine; $N \geq 50\%$; Δ ACH, change in coronary artery diameter in response to acetylcholine; $N > 0\%$; Δ NTG, change in coronary artery diameter in response to nitroglycerine, $N > 20\%$.

Table 2 Prior and case pregnancy data

Case	Age at pregnancy	Obstetrical history	History of spontaneous miscarriage	Aspirin during pregnancy	Gestational Age (weeks)	Birth Weight (g)
1	34	G5P3A1	Yes	Yes	37 4/7	2265
2	35	G4P2A1	Yes	Yes	35 1/7	2665
3	36	G4P2A1	Yes	Yes	40 5/7	3286
4	37	G3P1A1	No	Yes	39 5/7	3969
5	29	G2P0A1	Yes	Yes	40 0/7	3560

Pre-term birth or small for gestational age birth weight are in bold.

A, abortus; G, gravida; P, para.

Table 3 Seattle Angina Questionnaire (SAQ) scores at baseline and at last available and following pregnancy

		Physical limitation	Angina stability	Angina frequency	Treatment satisfaction	Disease perception	Change from baseline to last available follow-up
Case 1	Baseline	47.20	100.00	80.00	87.50	58.30	↓
	10 months PP	41.70	25.00	60.00	81.30	41.70	
Case 2	Baseline	80.60	50.00	80.00	100.00	41.70	↑
	5 yrs. PP	91.70	100.00	80.00	100.00	91.70	
Case 3	Baseline	100.00	50.00	70.00	50.00	16.70	↑
	12 months PP	100.00	50.00	80.00	75.00	33.30	
Case 4	Baseline	66.70	50.00	70.00	81.30	75.00	↓
	15 wks. gest.	88.90	50.00	90.00	100.00	66.70	
	4 yrs. PP	86.10	50.00	60.00	66.70	58.30	

SAQ, Seattle Angina Questionnaire—A higher SAQ Score in each domain is better; PP, post-partum; yrs., years; wks., weeks; gest., gestation; ↓, decline in SAQ scores; ↑, improvement in SAQ scores.

decreased foetal movements and non-reassuring biophysical profile, giving birth to a female child weighing 2665 grams at 35 weeks' gestation. Both SAQ scores and functional capacity were improved at 5 year follow-up (Tables 3 and 4).

Case 3

This 35-year-old G3P2A1 (three uncomplicated pregnancies delivered at term and one spontaneous miscarriage) woman with no

previous medical history initially presented with angina. On physical examination, vital signs were within normal range. Cardio-pulmonary auscultation and peripheral pulses were normal with no signs of volume overload. She underwent exercise cardiac single photon emission computed tomography (SPECT) and was found to have 1.65 mm ST segment depression on exercise electrocardiogram (ECG). Coronary microvascular dysfunction was evident by one of four abnormal pathways (Table 1). She was not on any beta-blockers

Table 4 Duke Activity Status Inventory (DASI) estimated Metabolic Estimate (METS) functional capacity at baseline and following pregnancy

	Baseline	During pregnancy	Last available post-pregnancy	Last available time post-pregnancy (years)
Case 1	3.60	—	4.0 ^a	0.83
Case 2	2.30	—	9.40	5
Case 3	10.70	—	12.30	1
Case 4	10.00	12.10	6.20 ^a	4
Case 5	5.40	—	2.80	0.58

^aDASI questionnaire incomplete, estimated using chart review/SAQ questionnaire. METS, metabolic equivalents.

prior to conceiving. She became pregnant 6 months after her CMD diagnosis. Self-reported frequency of angina was stable throughout pregnancy. There were no APO and she delivered a healthy female child weighing 3286 g at 40 weeks' gestation. Both SAQ scores and functional capacity were improved at 1-year follow-up (Tables 3 and 4).

Case 4

This 35-year-old G2P1A1 (one uncomplicated pregnancy delivered at term and one therapeutic abortion) woman with no previous medical history initially presented with persistent angina. On physical examination, vital signs were within normal range. Cardio-pulmonary auscultation and peripheral pulses were normal with no signs of volume overload. She underwent exercise cardiac SPECT which showed 12% reversible defect in the mid-distal anterior wall. Coronary microvascular dysfunction was diagnosed with three of four abnormal pathways (Table 1). Carvedilol was switched to labetalol because she was planning to conceive, and she became pregnant 1 year after her CMD diagnosis. Self-reported frequency of angina improved during pregnancy and labetalol was stopped. She did not experience any APO and delivered a female infant weighing 3969 g at 39 weeks' gestation. Four of five SAQ scores improved during pregnancy but deteriorated at last available 4 year follow-up, as did functional capacity (Tables 3 and 4).

Case 5

This 26-year-old G1P0A1 (one previous spontaneous miscarriage) with no previous medical history presented with angina. On physical examination, vital signs were within normal range. Cardio-pulmonary auscultation and peripheral pulses were normal with no signs of volume overload. She underwent stress CMRI which showed circumferential stress-induced hypoperfusion. Coronary microvascular dysfunction involved three of four abnormal pathways (Table 1). Labetalol was prescribed given her plan to conceive and she became pregnant approximately 1 year after CMD diagnosis. At 7 weeks' gestation, she visited the emergency department for worsened angina. ECG was non-ischaemic and serial troponin levels were negative. Labetalol was titrated to 100 mg PO TID at 37 weeks' gestation and continued throughout her pregnancy for angina. Her pregnancy was otherwise uncomplicated and she delivered a healthy male child

weighing 3560 g at 40 weeks' gestation. Baseline SAQ angina scores were unavailable for this woman. Functional capacity was worse 7 months after pregnancy (Table 4).

Discussion

To our knowledge, this is the first case series examining cardiovascular and pregnancy outcomes in women with CMD. Adverse maternal cardiovascular outcomes during pregnancy were uncommon in this case series, with self-reported increase of angina in only one woman. This finding mirrors the occurrence of angina requiring medical therapy during pregnancy in women with established obstructive CAD. In a series of 43 women who had a total of 50 pregnancies with a history of obstructive CAD or previous myocardial infarction, 8 women (19%), experienced increasing angina during pregnancy, with 2 requiring anti-anginal therapy, and 1 requiring hospitalization for serial biomarkers.³ High circulating levels of endogenous oestrogen and progesterone during pregnancy may limit the occurrence and frequency of angina, as our small randomized controlled-trial has previously shown that exogenous hormonal therapy can improve angina in women with CMD.⁹

Three women (60%) with CMD reported either worsening symptoms, decreased functional capacity, or both after pregnancy. Both persistent chest pain and poor functional capacity are associated to adverse events in this population.¹⁰ Pregnancy represents an important haemodynamic stress associated with a higher risk of unfavourable outcomes in numerous cardiac conditions at long-term follow-up. Whether it independently accelerates CMD or directly affects long-term functional status remains unclear and women should be appropriately counselled.

Although this is a relatively small case series, the fertility rate was lower than the national average of 62.0 births per 1000 women.¹¹ Lower fertility rates and higher rates of APO suggest that CMD, in combination with other factors, may play a role in pregnancy outcomes. The lower fertility rate observed in women with CMD may be secondary to overall coronary microvascular disease severity or personal choice. Angiotensin enzyme converting-inhibitors, ARB, and statins, used to treat CMD, are considered teratogenic. Beta-blockers, an important anti-anginal therapy, have been associated to foetal growth retardation.¹² It is possible that some women who

improve on these therapies decide to continue treatment rather than pursue pregnancy. Only one of five women in this case series was using contraception and had an unplanned pregnancy. Previous reports of women with INOCA found that 44% reported prior oral contraceptive use, compared with 29% in the general population, suggesting that uptake of contraception may be higher in this population.^{13,14}

The occurrence of APO in two of the five women (40%) and a history of spontaneous miscarriages in four of the five women (80%) are higher than the general population prevalence of 10%,¹¹ and 31%,¹⁵ respectively. Although a history of miscarriages or APOs has not been associated to evidence of CMD diagnosed using dipyridamole stress echo measured CFR,¹⁶ this modality is limited to the assessment of endothelial-independent CMD, and endothelial-dependent pathways may be primarily involved in APO, as suggested by findings in women with pre-eclampsia.⁴ Both women who experienced APO had a concomitant diagnosis of SLE, a potential confounder in our observations, and condition associated with both CMD¹⁷ and APO,¹⁸ in which abnormal uterine Doppler flows are associated with the occurrence of foetal loss, foetal growth restriction, and preterm birth.¹⁸ The endometrium is supplied by spiral arterioles, measuring 200 µm in the non-gravid uterus,¹⁹ and may share similarities with the coronary microvasculature, including vasoactive substance activity and response, such as the L-arginine-NO pathway, which mediates vasodilatation in both the coronary arteries²⁰ as well as the uterine and placental vessels.²¹ Conditions affecting microvascular bed function such as SLE and CMD may contribute to poor placental oxygenation and inadequate uterine blood flow through abnormalities in small vessel vasoactivity and function.

Coronary microvascular dysfunction, which is associated to microvascular dysfunction in other organs,²² may be a surrogate for functional anomalies in the uterine microvasculature, potentially dysregulating mechanisms responsible for vascular remodelling and placental development. In an animal study examining the L-arginine-NO pathway, endothelial-NO-synthase-enzyme knockout mice failed to show a normal decrease in uterine artery resistance.²³ Although these findings remain to be confirmed in human studies, and uterine Doppler was not performed in our patients, NO pathways, which are often abnormal in CMD, may be altered in the uterine microvasculature of women with established CMD and contribute to spontaneous miscarriage and APOs.

Conclusions

In this first case series of five women with confirmed CMD who became pregnant, frequency of angina remained stable during pregnancy in most patients, with no occurrence of adverse maternal cardiovascular outcomes. Overall, 80% of women reported a previous spontaneous miscarriage and 40% experienced an APO. Given the high prevalence of SLE in this series, we might hypothesize an interplay between SLE and CMD in microvascular dysfunction, which along with high levels of circulating hormones during pregnancy, may potentially explain our findings. Larger studies are needed to further explore whether pregnancy has long-term effects on functional status in this population.

Lead author biography



Dr Christine Pacheco completed medical school, Internal Medicine and Adult Cardiology fellowship training at University of Montreal, and then pursued an advanced fellowship in Women's Heart Health at the Cedars-Sinai in Los Angeles. Her clinical and research interests include coronary microvascular dysfunction, myocardial infarction in women, and pregnancy-related cardiovascular disease.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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