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Pregnancy in women with a history of Kawasaki disease: management and outcomes

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Objective To characterise the obstetrical management and outcomes in a series of women with a history of Kawasaki disease (KD) in childhood.

Design Retrospective case series.

Setting Tertiary healthcare setting in the USA.

Population Women with a history of KD in childhood.

Methods Women completed a detailed health questionnaire and participated in research imaging studies as part of the San Diego Adult KD Collaborative Study.

Main outcome measures Obstetrical management, complications during pregnancy and delivery, and infant outcomes.

Results Ten women with a history of KD in childhood carried a total of 21 pregnancies to term. There were no cardiovascular complications during labour and delivery despite important cardiovascular abnormalities in four of the ten subjects. Pregnancy was complicated by pre-eclampsia and the post-partum course

was complicated by haemorrhage in one subject each. Two of the 21 progeny subsequently developed KD.

Conclusions Women with important cardiovascular sequelae from KD in childhood should be managed by a team that includes both a maternal–fetal medicine specialist and a cardiologist.

Pre-pregnancy counselling should include delineation of the woman's current functional and structural cardiovascular status and appropriate adjustment of medications, but excellent outcomes are possible with appropriate care. Review of the English and Japanese literature on KD and pregnancy revealed the occurrence of myocardial infarction during pregnancy in women with missed KD and aneurysms that were not diagnosed until their acute event. Our study highlights the need for counselling with regard to the increased genetic risk of KD in offspring born to these mothers.

Keywords Anticoagulation, coronary artery aneurysms, Kawasaki disease, pregnancy, vasculitis.

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Introduction

A growing number of women with a history of Kawasaki disease (KD) are reaching child-bearing age, and little information is available to guide the obstetrical care and management of this patient population. KD, a self-limited vasculitis affecting the coronary arteries, and the most common cause of acquired heart disease in children, was first recognised in Japan following World War II, and is being diagnosed with increasing frequency among children in Asia, the USA and Western Europe.^{1–4} System dynamic models suggest that, by 2030, one in every 1600 adults in

the USA will have suffered from KD.⁵ KD is diagnosed by a constellation of clinical signs, with supportive laboratory data suggesting high levels of inflammation. The clinical signs include the abrupt onset of high fever, accompanied by four of the five following criteria: polymorphous exanthem, oral changes including pharyngeal erythema, cracked fissured lips and a strawberry tongue, bilateral conjunctival injection, cervical lymphadenopathy, and extremity changes that include oedema, palm and sole erythema, and periungual desquamation in the convalescent phase.⁶ Without treatment, 25% of children will develop coronary artery aneurysms that are associated with a risk of thrombosis

and myocardial infarction.⁷ Over time, most coronary artery aneurysms develop thickened walls with heavy calcification, and rupture is virtually never seen.⁸ Because the aetiology of KD is unknown and the diagnosis is based solely on clinical criteria, many cases are missed and may present in adulthood with myocardial infarction, congestive heart failure or sudden death.^{9–11} Timely treatment with high-dose intravenous immunoglobulin (IVIG) and aspirin reduces the risk of aneurysms to 5%.¹² The long-term outcome for adults with a history of KD in childhood is only now being studied.⁹ Recently, coronary calcium scoring by non-contrast computed tomography (CT calcium score) has been used for the detection of silent coronary artery damage decades after KD.¹³ Adults with cardiovascular complications resulting from KD may require interventions including angioplasty with stent placement, coronary artery bypass grafting (CABG) or cardiac transplantation, and may require treatment with a variety of medications, including antiplatelet agents, systemic anticoagulation, statins and angiotensin receptor blockers.⁹ This case series encompasses the spectrum of cardiovascular abnormalities that may be encountered by the obstetrician in pregnant women with a history of KD in childhood, and provides perspectives on issues to be considered in the management of these women during pregnancy and delivery.

Methods

We administered a general health questionnaire and performed interviews and physical examinations on all female subjects who had been pregnant and were enrolled in the San Diego Adult Kawasaki Disease Collaborative Study at the Kawasaki Disease Research Center at the University of

California at San Diego (UCSD). Of the 130 enrolled subjects, 58 were women and ten had undergone at least one pregnancy. Data collection included demographic information, details of the initial history of KD, cardiovascular complications, medications, therapeutic interventions, cardiovascular risk factors, obstetrical history and pregnancy outcome. This protocol was approved by the Institutional Review Board at UCSD and all subjects gave their written informed consent. We completed a comprehensive review of the current literature in English and in Japanese using PubMed and the Japan Medical Abstracts Society with 'Kawasaki Disease' and 'pregnancy' as the search terms.

Results

The cardiovascular and obstetrical outcomes of ten women with a history of KD in childhood were reviewed. Four of the ten women had important cardiovascular sequelae from their KD, including coronary artery aneurysms (four subjects), myocardial infarction (two subjects) and CABG (three subjects) (Table 1). In three of the four women, these events occurred prior to their first pregnancy. In the fourth woman (Table 1, subject 10), who suffered four myocardial infarctions, two of these events occurred prior to her first pregnancy and the subsequent events were not temporally related to her subsequent pregnancy. Two of these four women were advised either not to become pregnant or to terminate their pregnancy in the first trimester by physicians who were unfamiliar with KD. Of the three subjects with cardiovascular sequelae who had assessment of their coronary artery calcium by CT, all had evidence of calcium deposition in the arterial wall (Table 1, Figure 1). During their eight pregnancies, all four women with

Table 1. Demographic and clinical characteristics and cardiovascular complications in women with a history of Kawasaki disease (KD) in childhood

Subject	Age at onset of KD (years)	Ethnicity	Treatment for acute KD	CA status	Complications	CT calcium volume score (mm ³)
1	0.5	Caucasian	Not treated, given aspirin	NI	None	0
2	1.5	Korean	Treated with steroids	NI	None	0
3	2	Hispanic	Treated with IVIG	NI	None	0
4	5	Hispanic	Treated with IVIG	NI	None	0
5	5	Caucasian	Not treated (missed KD)	+CAA	CABG (18 years)	NA
6	5	Caucasian	Not treated (missed KD)	+CAA	CABG (12 years)	2123
7	6	Caucasian	Treated, specifics unknown	NI	None	0
8	12	AA/Caucasian	Not treated (missed KD)	+CAA	MI (24 years), CABG (24 years)	8218
9	12	Caucasian	Late treatment	NI	None	NA
10	15	Caucasian	Late treatment	+CAA	MI × 4 (19, 20, 29 and 33 years)	234

AA, African-American; CA, coronary artery; CAA, coronary artery aneurysms; CABG, coronary artery bypass grafting; CT, computed tomography; IVIG, intravenous immunoglobulin; MI, myocardial infarction; NI, normal; NA, not available.

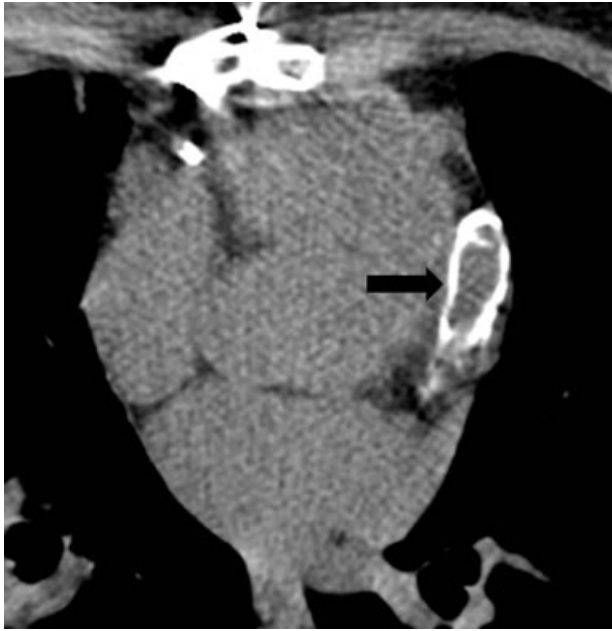


Figure 1. Computed tomography coronary artery calcium scan of a 44-year-old woman with a history of Kawasaki disease at 12 years of age, giant coronary artery aneurysms and a scan demonstrating severe coronary calcification of the left anterior descending artery (black arrow).

cardiovascular sequelae of KD were treated with aspirin, whereas three of the four women were also treated with enoxaparin (Table 2). None experienced cardiovascular complications during pregnancy. Two women had elective caesarean sections because of concerns for potential cardio-

vascular complications during labour. Of the five infants delivered vaginally, one required forceps-assisted delivery. The only obstetrical complication amongst these four women with aneurysms was post-partum haemorrhage requiring blood transfusion following caesarean section in one. Of note, this patient was restarted on heparin immediately post-partum, which may have contributed to the consequent haemorrhage. Of the eight infants born to these four mothers, all were carried to term and were healthy; one had trisomy 21.

Of the six women with no detectable cardiovascular sequelae from KD, no cardiovascular medications were prescribed during pregnancy and healthy infants were delivered by spontaneous vaginal delivery in five women and by caesarean section in one woman. One patient had premature labour at 24 weeks, but carried her infant to term; another patient had pre-eclampsia with a normal vaginal delivery at term.

Of the 21 infants delivered to the ten mothers in this series, two developed KD at ages 2 and 5 months. Both infants were treated with IVIG and had normal coronary artery internal dimensions as measured by echocardiography. One infant developed mild aortic root dilatation that subsequently resolved.

Discussion

Main findings

In our series of ten women with a history of KD in childhood, only one experienced an obstetrical complication of post-partum haemorrhage that was possibly related to the

Table 2. Obstetrical management and outcome of women with a history of Kawasaki disease in childhood

Subject	Gravidity/parity	Age at first pregnancy (years)	Medications during pregnancy	Delivery	Complications during pregnancy/delivery
1	G2P2002**	27	None	NVD	Pre-eclampsia with first pregnancy
2	G4P4004	31	None	NVD	Premature labour at 24 weeks of gestation with first pregnancy
3	G2P2002	18	None	NVD	None
4	G4P2022	28	None	NVD	None
5*	G5P4014	Unknown	Aspirin, enoxaparin	NVD	None
6*	G2P1011	32	Aspirin, enoxaparin	Forceps required, VD	None
7	G3P2012	29	None	1 NVD, 1 C-section	None
8*	G1P1001	41	Aspirin	C-section	None
9	G2P1011	28	None	NVD	None
10*	G2P2002	32	Aspirin, enoxaparin	C-section	Post-partum haemorrhage requiring blood transfusion with second pregnancy

C-section, caesarean section; NVD, normal vaginal delivery.

*Patients with significant cardiovascular abnormalities.

**Number of pregnancies with the following outcomes: term, premature, aborted, live birth.

premature re-institution of heparin therapy after delivery. Caesarean section was recommended for two women solely because of concerns for potential cardiovascular complications during labour. There are currently no systematically collected data on which to base recommendations for the management of pregnancy and delivery in this patient population. However, the outcomes with routine obstetrical management appear to be favourable.

Strengths and limitations

We recognise several strengths and limitations to our work. This is the first reported series of women with a history of KD in childhood whose cardiovascular status was systematically evaluated as part of a prospective study of outcomes in young adults after KD. However, the details of the obstetrical care of the patients were obtained from the patients, and therefore all of the caveats and potential biases of a retrospective study apply. In addition, our small sample size limits the strength of the conclusions that can be drawn.

Interpretation

A range of cardiovascular abnormalities can be encountered in young adults following KD in childhood. These may include coronary artery aneurysms with varying degrees of altered blood flow, coronary artery stenoses, myocardial ischaemia, myocardial fibrosis, congestive heart failure and valvular abnormalities, including stenosis and incompetence.^{14–17} Women with coronary artery aneurysms may have experienced myocardial infarction or have undergone interventions, including percutaneous coronary intervention with or without stenting, coronary bypass surgery or cardiac transplantation. All of these cardiovascular complications of KD pose potential risks to the mother during pregnancy, labour and delivery. In addition, medications used to manage the complications of KD may pose a risk to the fetus and must be assessed during pre-pregnancy screening. Most patients with aneurysms are treated with antiplatelet agents (aspirin or thienopyridines), and current recommendations are to treat patients with giant coronary artery aneurysms (defined as >8 mm in diameter) with warfarin because of the high risk of thrombosis caused by the altered haemodynamics within the aneurysm.^{6,18,19}

Japan is the country with the highest incidence of KD, although all racial groups may be affected. A comprehensive review of patients in the Japanese literature yielded 11 reports that detailed the management, delivery method and outcomes in 52 Japanese women with a history of KD (Table 3).^{20–30} All but two women had coronary artery aneurysms and three had undergone CABG. Of the 72 deliveries, 29 (40.3%) were caesarean sections. Obstetrical complications were reported in seven (9.7%) deliveries, including premature rupture of membranes, pre-term

labour and post-partum haemorrhage. Cardiovascular complications were reported in five (9.6%) women and included reduced ejection fraction in one, and chest pain, low oxygen saturation, premature ventricular beats and bradycardia among the remaining four women. Of the 72 infants, 63 (87.5%) were delivered at term and were healthy; two infants were delivered prematurely at 33 weeks by caesarean section because of maternal distress, described as chest pain, bradycardia and low oxygen saturation. Five additional infants were born prematurely. Two additional infants had congenital abnormalities consisting of ventricular septal defect and agenesis of the corpus callosum. The variation in obstetrical management in these women underscores the need for prospective studies that can better define the risks in this patient population and lead to the development of consistent management guidelines.

A review of women with a known or suspected history of KD residing outside of Japan revealed only four single-patient case reports^{31–34} (Table 3). All had coronary artery aneurysms. Collectively, these women gave birth to nine infants by vaginal delivery (eight infants) or caesarean section. One woman with an unknown history of KD suffered a myocardial infarction at 38 weeks of gestation, followed by vaginal delivery of a healthy infant. Coronary artery aneurysms were found and a history consistent with KD in childhood was elicited. Another woman with an unknown history of KD suffered a myocardial infarction at 20 weeks of gestation, was found to have coronary artery aneurysms and delivered a healthy infant at term. This woman delivered four subsequent infants vaginally and one infant by caesarean section without cardiovascular complications. The only obstetrical complication was pre-eclampsia in one woman, followed by mild hypertension in her second pregnancy. Of the nine infants born to these mothers, all were healthy and eight were delivered at term, whereas one was delivered at 35 weeks to the mother with pre-eclampsia. The two women who suffered myocardial infarction during pregnancy highlight the potential catastrophic outcomes in patients with missed KD in childhood whose cardiac condition is not appropriately managed during pregnancy.

Two of the ten women in our series gave birth to infants who went on to develop KD in the first year of life. Both mothers were unaware of the genetic component to susceptibility to KD and were unfamiliar with the characteristic clinical signs of KD because they had no personal memory of their illness in childhood. This underscores the need for appropriate counselling of mothers with respect to the genetic risk of KD in their offspring. KD is thought to occur in genetically susceptible children following environmental exposure to an unknown agent that triggers the immunological cascade that is recognised as acute KD. The genetic risk is determined by polymorphisms in a number

Table 3. Obstetrical management and outcome of 81 pregnancies in 55 women with a history of Kawasaki disease (KD) published in the English and Japanese language literature

Reference	Study design	Sample size	Coronary artery status of subjects	Mode of delivery	Cardiac complications	Obstetrical complications	Outcome
Nolan and Savage ³¹	Case report	1	History of KD-compatible illness in childhood, CAA	NVD	MI at 38 weeks, CAA by echocardiogram	None	38 weeks, healthy
Alam et al. ²⁰	Case report	1	Giant CAA with occluded RCA	C-section	None	None	40 weeks, healthy
Kurioka ²² (in Japanese)	Case report	1	History of KD-compatible illness in childhood, CAA of LMCA and stenosis of RCA	C-section	None	None	41 weeks, healthy
Arakawa et al. ²³	Case report	1	CAA	C-section	None	None	38 weeks, healthy
Tsuda ²⁴ (in Japanese)	Case report	G1P1	Giant CAA with stenosis	C-section	26 weeks, EF 47.1%	None	38 weeks, healthy
Iino ²⁵ (in Japanese)	Case report	G1P1	CAA and occlusion with collaterals	C-section	None	30 weeks, premature labour	37 weeks, healthy
Hayakawa and Katoh ²⁶	Case report	1	S/P CABG	NVD	None	37 weeks, PROM	Term, healthy
Shear and Leduc ³²	Case report	1	CAA	NVD	None	None	38 weeks, healthy
Tsuda ²⁷ (in Japanese.)	Case report	G1P1	CAA with stenosis and calcification	C-section (33 weeks 6 days)	Chest pain, PVC, bradycardia, low oxygen saturation	Premature birth	33 weeks, 1855 g, Apgar 6/7/7
McAndrew et al. ³⁴	Case report	G5P5	KD history unknown, CAA	4 NVD, 1 C-section	Cardiac arrest at 20 weeks of gestation; CAA at angiography	None	Term infants, healthy
Tatsumi ³⁰ (in Japanese)	Case report	4	CAA, CABG CAA, CABG Giant CAA	NVD NVD C-section (33 weeks 6 days)	None 32 weeks, PVC Dyspnoea, low oxygen saturation	None None None	37 weeks, healthy 39 weeks, healthy 33 weeks, healthy
Tsuda et al. ²⁹	Retrospective case series	10 subjects 13 deliveries	Giant CAA All with CAA	NVD 10 NVD, 3 C-sections	Occasional PVC, 5-minutes fetal bradycardia before delivery None	None 1 PROM with vaginal haemorrhage	39 weeks, healthy 12 term infants, 1 premature infant
Tsuda et al. ²⁸	Questionnaire completed by physician	30 women 46 deliveries	All with CAA	27 NVD, 19 C-sections	None	1 PROM 1 post-partum haemorrhage on heparin	40 term infants, 1 VSD, 1 agenesis of the corpus callosum, 4 premature infants

Table 3. (Continued)

Reference	Study design	Sample size	Coronary artery status of subjects	Mode of delivery	Cardiac complications	Obstetrical complications	Outcome
Hibbard et al. ³³	Case report	G2P2	CAA	NVD	None	G1 pre-eclampsia G2 mild hypertension	35 weeks 37 weeks
Kobara ²¹ (in Japanese).	Case report	G2P2	Giant CAA with stenosis and calcification	NVD	None	1 PROM (37 weeks 1 day)	37 weeks, healthy 38 weeks, healthy

CAA, coronary artery aneurysm; CABG, coronary artery bypass graft; C-section, caesarean section; EF, ejection fraction; LMCA, left main coronary artery; NVD, normal vaginal delivery; PROM, premature rupture of membranes; PVC, premature ventricular contraction; RCA, right coronary artery; S/P, status post; VSD, ventricular septal defect.

of different biological pathways and no risk prediction algorithm is currently available.^{35,36} Japanese data suggest a two-fold increased risk of a history of KD among parents of children diagnosed with KD.³⁷ The familial occurrence of KD is also well documented in pedigrees from North America.³⁸ Although there is no prenatal test to assess KD susceptibility, it is important for women to receive the information that susceptibility to KD has a genetic basis and that their offspring may be at increased risk.

Conclusions

There are three groups of women with a history of KD who may present to the obstetrician for the management of pregnancy: women with normal echocardiograms during the acute illness, women with coronary artery abnormalities and women with a history of KD whose cardiovascular status is unknown. Management during pregnancy should be directed collaboratively by maternal and fetal medicine and cardiology teams. For women with normal echocardiograms during acute KD, no screening or special considerations appear to be warranted and routine obstetric management is appropriate.^{9,10} For women contemplating pregnancy who have a history of KD associated with cardiovascular abnormalities, consultation with a cardiologist is advised. Late rupture of aneurysms does not occur and decisions regarding the safety of pregnancy should follow the same principles as for any other patient with cardiovascular compromise. A stress echocardiogram should be performed as part of pre-pregnancy screening or during the first trimester of pregnancy. Assessment of the coronary arteries prior to pregnancy should be performed with a CT angiogram or MR angiogram if performed after conception. Adjustment of medications must also be addressed, including the substitution of enoxaparin for warfarin and the discontinuation of statins. Standard guidelines for the management of women with cardiovascular compromise can be applied to this patient population. In the absence of congestive heart failure or severe ischaemia, there is no indication for pregnancy termination solely on the basis of maternal cardiovascular disease as a result of KD. For women with a history of KD and unknown cardiovascular status, a stress echocardiogram and preconception CT calcium score may be useful to screen for coronary artery abnormalities. A positive calcium score should prompt further imaging by CT or MR angiogram. In summary, with appropriate surveillance and management, the majority of women with a history of KD can successfully carry a pregnancy to term and have a normal labour and delivery.

Disclosure of interests

No conflicts of interest to report.

Contribution to authorship

CTG and JCB planned and coordinated the project, analyzed the patient data and reviewed the English literature. SJ-F was instrumental in gathering patient information and coordinating communication with the study participants. LBD and JBG served as senior cardiologists and adult KD expert consultants. Their participation involved reviewing and editing the manuscript, as well as providing subjects for the study from their San Diego Adult KD Collaborative Study. MT served as the senior OBGYN consultant, offering insight and expertise regarding obstetrical management, as well as reviewing and editing the manuscript. CS and TM reviewed and translated all of the Japanese literature on KD and pregnancy into English to enhance our literature search. AMK performed the imaging studies on all subjects, provided the images of coronary aneurysms for this report and reviewed the manuscript.

Details of ethics approval

This study was first reviewed and approved by the Institutional Review Board at UCSD, Protocol # 090902 on 07/02/2009.

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