Pregnancy and breast cancer in a patient with complicated Kawasaki Disease, as if one problem was not enough: a case report

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Case summary

We report on the pregnancy outcome of a 30-year-old woman with KD who was successfully resuscitated for ventricular tachycardia 3 years before. At that time, bypass surgery and later implantable cardioverter-defibrillator implantation were performed because of thrombocytically occluded calcified giant coronary aneurysms. The pregnancy course was initially uncomplicated, however, at 31 weeks of gestation, left-sided breast cancer was diagnosed. Weighing maximum therapeutic efficacy against acceptable foetal and maternal cardiotoxic risk, our multidisciplinary team decided on neoadjuvant chemotherapy. The mother and foetus tolerated the therapy well. However, at 36 weeks of gestation, due to HELLP (haemolysis, elevated liver, low platelets) syndrome, a caesarean section had to be performed. The newborn was healthy with good APGAR (appearance, pulse, grimace, activity, respiration) scores. Three weeks after delivery, chemotherapy was restarted and at Week 4 after the caesarean section, the tumour was no more detectable.

Discussion

We discuss data on pregnancy and KD and outline that pregnancy can be considered if the clinical condition is good and left ventricular function is preserved. We also address possible therapeutic approaches and care for breast cancer in pregnancy and co-existing cardiovascular disease. The extraordinary importance of interdisciplinary cooperation between different disciplines in such complex clinical disease conditions is emphasized.

Keywords

Case report • Kawasaki syndrome • Pregnancy • Coronary aneurysms • Breast cancer • HELLP

ESC Curriculum

9.8 Pregnancy with cardiac symptoms or disease • 3.1 Coronary artery disease • 5.6 Ventricular arrhythmia
About one-fourth of the patients develop coronary artery aneurysms or ectasia associated with lifelong risk for thrombotic occlusions and myocardial infarction (MI). Long-term prognosis depends on the extent of coronary involvement, with coronary aneurysm size appearing to be the strongest predictor of major cardiac events. One of the patients developed coronary aneurysms at the ostium of the right and left coronary arteries were noted with a computer tomography (CT)-morphological diameter of 15 mm, raising the high suspicion of Kawasaki syndrome (Figure 1). Positron emission tomography–CT excluded persistent inflammatory activity. A discussion with the heart team, bypass graft surgery with the left internal mammary artery (LIMA) on LAD and right internal mammary artery (RIMA) via saphenous vein interposition on RCA was performed. The patient was followed for 8 months, the patient recovered well, and exercise tolerance was very good. She did regular endurance training (running) and was in good clinical exercise status.

Two years later, the patient expressed a strong desire to have children. A risk assessment was performed to evaluate whether pregnancy could be considered. Physical examination showed no abnormalities. Blood pressure (107/70 mmHg) and heart rate (71/min) were within normal ranges. Electrocardiography (ECG) showed sinus rhythm between 60 and 70/min, delayed R progression, and q in V1-V3. Laboratory chemistry showed low N-terminal pro-brain natriuretic peptide (NTproBNP 117 ng/L). Echocardiography revealed low-normal systolic left ventricular ejection function (LVEF 50%) with minor anteroseptal wall motion abnormalities. Strain analysis showed low-normal global strain (16.5%) with main reduction basal segments. Vascular duplex sonography revealed normal cervical and abdominal vessels. From the summary of findings and in view of the patient being symptom-free and having a good exercise capacity, we assessed—on the basis of the current literature—the risk of pregnancy as increased, but acceptable. After information about risks, necessary medication changes, and the need for close interdisciplinary care, the patient decided to become pregnant. In June 2021, she presented at Week 5 of pregnancy. We switched rivaroxaban to body-weight-adjusted dose.
low-molecular-weight heparin (tinzaparin). Statin therapy was discontinued, and aspirin (100 mg/d) and metoprolol were maintained. Interdisciplinary care with clinical controls at four weekly intervals was performed. The pregnancy was without any complications until the third trimester. The foetus developed well.

Unfortunately, at 31 weeks of gestation, breast cancer of non-special-type (NST) stage cT3 pN+ (histologically proven lymph node metastasis after ultrasound-guided biopsy) with intermediate differentiation (G2), oestrogen receptor (ER) 30%, progesterone receptor (PR) 20%, human epidermal growth factor-2 (HER-2) not overexpressed (1+), proliferation index (Ki67) 25%, PD-L1-negative (IC 5%, CPS score 5) was discovered in the left breast (Figure 2). In the interdisciplinary tumour board consisting of gynecologists, oncologists, cardiologists, obstetricians, coagulation physicians, and neonatologists, the consensus was reached for immediate neoadjuvant chemotherapy with epirubicin and cyclophosphamide (EC) in reduced dosage (30 mg/m², 200 mg/m²) and weekly application. Then, an elective caesarean section and postpartum surgery after completion of neoadjuvant chemotherapy (after 12 cycles with weekly EC, further 12 cycles with weekly paclitaxel were planned) were scheduled. The advantages and disadvantages of the various therapy options in pregnancy were discussed in detail with the patient, who was very discriminating and well-informed. After weighing the risk for her and her unborn child, she decided to follow the recommendation for neoadjuvant chemotherapy. The initial course was uneventful, the patient and foetus tolerated chemotherapy well. Bi-weekly clinical and echocardiographic follow-ups showed stable pump function and global longitudinal strain (GLS). Cardiac markers were within the normal

Figure 1 Computated tomography. Sagittal (A) and axial (B) contrast computed tomography images and three-dimensional reconstructions (C, D) showing coronary aneurysms of the right coronary artery (white arrows in A, C) and left anterior descending (white arrows in B, D) and right internal mammary artery bypass graft (yellow arrow in C) and left internal mammary artery bypass graft (yellow arrow in D).
range. The foetus was closely monitored by cardiotocography and sonography.

At 35 weeks, after five cycles of chemotherapy, the patient presented with acute upper abdominal and thoracic pain, dyspnoea, and tachycardia. Her blood pressure was normal. ECG and echocardiography revealed no new abnormal findings, and ICD control showed no events. However, laboratory chemistry detected thrombocytopenia (down to 50 000/µL) and elevated liver enzymes (glutamic pyruvic transaminase: 1922 U/L; glutamic oxaloacetic transaminase: 3094 U/L) and inflammatory parameters (c-reactive protein: 114.6 mg/L), so HELLP (haemolysis, elevated liver, low platelets) syndrome was suspected and an emergency caesarean section was performed.

A healthy newborn was delivered with good APGAR (appearance, pulse, grimace, activity, respiration) scores (9, 9, 10) and pH values. The patient recovered well and liver enzymes and platelets normalized rapidly. Comprehensive diagnostics to exclude metastases (skeletal scintigraphy, CT of thorax, abdomen, and pelvis) were performed without any detection of skeletal or distant metastases. Three weeks after the caesarean section, chemotherapy was restarted on an outpatient basis. After six cycles of EC, at Week 4 after the caesarean section, the breast tumour was clinically, sonographically and on breast magnetic resonance imaging (MRI) no longer detectable next to the clip marker placed within the tumour before neoadjuvant chemotherapy had been started. The patient had complete clinical and radiological remission. After 10 cycles of EC, chemotherapy was switched to paclitaxel for another 12 cycles. Breast-conserving surgery or total mastectomy will be considered during follow-up. At 14 weeks of postpartum, echocardiography showed stable findings with mildly reduced systolic left ventricular function (LVEF 47%) and global strain (GLS −14%). Cardiac markers were normal (NTproBNP 68 ng/L; troponin T 9 ng/L). The patient denied any cardiac symptoms.

Discussion

Kawasaki Disease and pregnancy
KD with coronary artery involvement and aneurysms may pose a special risk for the mother during pregnancy, labor, and delivery. Pregnancy-related physiologic changes such as an increase in blood volume, heart rate, and cardiac output as well as hormonal influences on the vessel wall and the hypercoagulable state including impaired fibrinolysis predispose to particularly elevated risk.

Still, now, there is sparse information on the management and outcome of pregnancy in KD. Only a few small series and single reports have been published. In 2014, Gordon et al. described cardiovascular and obstetric outcomes in 21 pregnancies from 10 women with KD.
from a single institution registry, two of whom had a previous myocardial infarction (MI), and three had a history of bypass surgery. Apart from pre-eclampsia in one woman and postpartum hemorrhage in another, there were no relevant cardiovascular complications. The authors additionally summarized the results of 81 pregnancies in 55 patients from the English and Japanese literature, including data from a nationwide survey in Japan. All but one woman had coronary aneurysms, and three patients had previously undergone bypass surgery. Five patients (9.6%) experienced cardiovascular symptoms/events, such as a decrease in ejection fraction, chest pain, low oxygen saturation, bradycardia, or premature ventricular beats during pregnancy. Two patients with previously unknown KD, one at 38 weeks and the other at 20 weeks of pregnancy, suffered from MI.

More recently, data from a Japanese cohort of 19 pregnancies in 13 women with KD have been published. Three of these patients had undergone interventions before pregnancy, therefrom two bypass grafts. Cardiovascular events occurred in four patients during the postpartum period. Two complained of chest discomfort after delivery without signs of ischemia, one developed a decrease in ejection fraction (EF) to 40% and non-sustained VT and another had recurrent tachyarrhythmia and subsequently non-sustained VT.

In summary, the studies show that KD is associated with a substantial risk of cardiac events during pregnancy; however, most complications can generally be well managed. Rupture of the aneurysm and/or dissection of the altered coronary arteries during pregnancy and delivery are hypothetical risks, but there are no reports of these complications in the literature. MI and one resuscitation have been described in a formerly unknown KD; however, mother and child have had a good prognosis.

Unfortunately, the data do not allow for defining specific constellations that predict increased complication rates during pregnancy. In analogy to coronary artery disease (CAD) studies, previous acute coronary syndrome might be associated with adverse events. Bypass-operated patients do not appear to have a worse outcome. The studies indicate that a good pre-pregnancy condition, as in our patient, is associated with a favorable course. The ESC (European Society of Cardiology) Guidelines for the Management of Cardiovascular Disease in Pregnancy similarly emphasize that pregnancy can be considered in patients with known CAD in the absence of residual ischemia and clinical signs of LV dysfunction. To our knowledge, the present case is the first to report on a successful pregnancy in a KD patient with a dramatic cardiac history including resuscitation, bypass surgery for thrombotic occlusion of two coronary arteries, and ICD implantation.

Regarding drug therapy, medication should be adjusted according to the general principles for pregnancy, which means that embrototoxic and fetotoxic substances must be discontinued. There are no robust data on the management of antithrombotic therapy. The guidelines for the treatment of KD outside pregnancy emphasize that the focus of long-term drug therapy should be the prevention of thrombotic complications. There is consensus that lifelong low-dose aspirin therapy should be given, and the addition of anticoagulation is recommended in patients with giant coronary artery aneurysms (>8 mm). In published studies, aspirin was administered during pregnancy in only about half of the patients; and anticoagulation was performed even less frequently. In a study conducted on a series of 10 women, Gordon et al. found that 4 women with prior coronary bypass graft surgery and/or MI were treated with aspirin, and 3 of them were treated along with enoxaparin. None experienced cardiovascular complications, and one postpartum hemorrhage requiring blood transfusion occurred. Our patient has been treated with aspirin and low-molecular-weight heparin, because of giant aneurysms and mild thrombophilia related to the underlying KD. With the exception of abdominal wall hematoma in the surgical area of the caesarean section, there were no bleeding complications.

In other studies, vaginal delivery was possible in most asymptomatic KD patients with preserved EF. Caesarean section was usually required because of obstetrical indications. However, in some patients, it was performed because of maternal discomfort (chest pain, arrhythmias) or concern for potential cardiovascular complications in case of prior MI. In our patient, the pregnancy heart team decided on a caesarean section due to the complex and complicated history, for better management in the presence of antithrombotic therapy, and at the patient’s wish. As outlined, an emergency caesarean section was finally performed at 36 weeks because of HELLP syndrome.

Interdisciplinary collaboration between specialties during pregnancy and delivery is crucial for a successful outcome. Guidelines recommend that pre-pregnancy counselling and management of pregnancy and delivery should be conducted in a tertiary expert center by a pregnancy heart team. The minimum requirements are a cardiologist, an obstetrician, and an anesthesiologist, plus additional experts depending on the individual situation. In our patient with a new discovery of breast cancer, comprehensive expertise from the specialties of oncology, hemostaseology, and neonatology was required.

Breast cancer, pregnancy, and heart disease

During the last trimester of pregnancy, our patient was diagnosed with a long-term differentiated carcinoma of the NST with infiltration of the left axillary lymph nodes. Breast cancer in pregnancy accounts for 0.2–2.6% of all malignant breast tumours and 7–15% of premenopausal breast cancer occurs during pregnancy. With an incidence of 1/1000 pregnancies, it is the most frequent entity of pregnancy-associated malignant tumours. Invasive carcinoma of NST is the most common histological type in pregnancy. Nodal involvement is seen more often in pregnant than in non-pregnant women and the tumour is often large. Compared with postmenopausal tumours, breast cancer in young women often lacks hormone receptor expression and is HER-2 negative (‘triple negative’). Our patient had a luminal B-like tumour type with ER 30%, PR 20%, Ki67 25%, and HER-2 negative.

Diagnosis in pregnancy is primarily based on sonography and biopsy. Mammography may be considered with appropriate abdominal shielding but because of the high density of the breast, sensitivity is low. Environmental diagnostics using ionizing radiation and scintigraphy to detect the sentinel lymph node should be avoided, especially in the first trimester. MRI is an option, but the gadolinium-based contrast agents cross the placenta and have been associated with foetal abnormalities in animal studies. Furthermore, the patient had to lie on her stomach during the breast MRI. This could cause problems during the later weeks of pregnancy. Therefore, MRI should be used with caution.

Therapeutic options include primary breast surgery or neoadjuvant chemotherapy. While the risk of foetal malformation is high during the first trimester, chemotherapy is associated with acceptable risk in the second and third trimesters although growth restriction may occur. Anthracyclines, one of the standard chemotherapies in breast cancer therapy, may be used in pregnancy with close monitoring of the mother and foetus. Taxanes and cyclophosphamide may also be given. Anti-hormonal therapy such as tamoxifen and the HER-2-inhibitor trastuzumab are contraindicated because of the high incidence of congenital abnormalities, namely oligo/anhydramnion. Regarding breast cancer outcome, there appears to be no difference between pregnant and non-pregnant patients. The poorer outcome described in older studies has been attributed to delayed diagnosis and treatment due to pregnancy. Most of the sparse foetal outcome data showed no increased risk of congenital abnormalities, mental retardation, or cardiotoxicity in the long-term follow-up. However, there were reports of stillbirths and neonatal deaths.
Weighing maximum therapeutic efficacy (taken into account stage and histological type) against acceptable foetal and maternal cardiotoxic risk, our multidisciplinary team decided to opt for neoadjuvant chemotherapy. This decision was made primarily to check the chemotherapy sensitivity of the tumour and to reduce the tumour and lymph node metastases. In case of non-pathological complete remission after neoadjuvant chemotherapy, targeted post-neoadjuvant therapy may result in a survival benefit. In the case of primary surgery, the absence of this information may lead to a prognostic decline. Doxorubicin/cyclophosphamide or epirubicin/cyclophosphamide (EC) are the best-studied chemotherapeutical substances in pregnancy and therefore the first choice.\(^\text{12}\) Epirubicin was chosen because it is non-inferior to doxorubicin but associated with lower cardiotoxic risk.\(^\text{16}\) After five cycles of chemotherapy, HELLP syndrome occurred. This complication is observed in 0.5–0.9% of pregnancies and is often seen in patients with severe preeclampsia.\(^\text{17}\) However, it can also occur without hypertensive complications as in our patient.\(^\text{17}\) To our knowledge, there are no data regarding HELLP syndrome in the context of chemotherapy or KD.

In conclusion, we show that pregnancy can be considered in severe KD if the clinical condition is good and LV function is preserved. In our case, neonatal and maternal cardiac outcomes were good, despite additional serious complicating conditions such as breast cancer requiring chemotherapy and HELLP syndrome requiring an emergency caesarean section. This case report highlights that interdisciplinary collaboration between the specialties involved in the mother’s care during pregnancy and delivery is crucial for a successful outcome.

**Lead author biography**

Gina Barzen is following residency in cardiology and internal medicine at the Charité, Universitätsmedizin Berlin, Germany since 2019. She studied medicine at the University of Greifswald and graduated in 2019.

**Supplementary material**

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

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent:** The patient has given her written consent to the submission and publication of the case data including the images and videos according to COPE guidelines.

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