



## Factors Related to Congenital Heart Disease in Offspring from Women with Rheumatic Heart Disease: Case reports from Moi Teaching and Referral Hospital, Eldoret, Kenya

Philippe PA<sup>1\*</sup>, Orang'o EO<sup>1</sup>, Barasa FA<sup>2</sup>

<sup>1</sup>Department of Reproductive Health, Moi University School of Medicine, P. O Box 4606-30100, Eldoret, Kenya

<sup>2</sup>Department of Cardiology, Moi Teaching and Referral Hospital - Eldoret, Kenya, P.O Box 3-30100, Nandi Road, Eldoret, Kenya

Corresponding Author: **Dr. Philippe Amubwuomombe Poli, MD**

**Address:** Department of Reproductive Health, Moi University School of Medicine. P. O Box 4606-30100, Eldoret, Kenya;

E-mail: [philippe\\_poli@yahoo.fr](mailto:philippe_poli@yahoo.fr)

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### Abstract

Maternal exposure to environmental factors has been reported to be associated with birth defects. Congenital heart defects are the most common and are associated with high morbidity and mortality in offspring. However, the relation of maternal rheumatic heart disease to congenital heart defects in the offspring is a rare event not yet reported. The authors report 2 cases of infants with congenital heart defects born from mothers with rheumatic heart disease. This study highlights factors related to congenital heart defects in both newborns.

### Keywords

Congenital Heart Disease; Rheumatic Heart Disease; Offspring

### Introduction

Birth defects are a global burden. Of these, congenital heart defects (CHDs) are among the most common congenital malformations. Although there is an increased incidence of CHD in Western countries, there is a paucity of data in low- and middle-income countries (LMICs) regarding congenital heart defects [1,2]. To date, congenital heart defects are considered as multifactorial disease and are predominantly reported among infants with a family history of CHDs. There is limited data upon factors related to neonatal congenital heart defects in women with rheumatic heart disease (RHD). The challenges related to the diagnosis in the context of resource-

limited settings and factors related to CHDs are extensively discussed in this paper. The current findings were obtained from a large study involving pregnant women with cardiac disease at Moi Teaching and Referral Hospital, the second largest national hospital in Kenya, located in Rift Valley.

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The first patient was 38 years old, gravida 7 paras 6 at 36 weeks of gestation, transferred from a primary healthcare facility for dyspnoea, palpitation, bilateral lower limb oedema, and weight loss. She had had 6 successful homebirths, and this was her first admission to the hospital. Her past medical and family

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histories were unremarkable; however, she was illiterate and did not have health insurance. Vital signs were unremarkable except for the pulse rate, which was as high as 155 beats per minute. Her body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) was 16 kg/m<sup>2</sup> (indicating underweight).

The echocardiography showed features of rheumatic heart disease with severe mitral stenosis and pulmonary hypertension. The electrocardiogram showed features of atrial fibrillation. Obstetric ultrasonography showed a single intrauterine pregnancy at 36 weeks of gestation without fetal anatomical anomalies. She was put on subcutaneous clexane 40mg (enoxaparin sodium) daily for prophylaxis of venous thromboembolism, digoxin 0.125 mg twice daily, furosemide 40 mg twice daily, and monthly benzathine penicillin. The patient was also managed for anemia and severe malnutrition. At 36 weeks and 5 days, she went into labor and delivered a female infant weighing 2000 grams, with an Apgar score of 8 at 5 minutes. The neonate was admitted to the newborn care unit for hypoxia and acute respiratory distress. On the 7th day following birth, the newborn exhibited persistent hypoxia, respiratory distress, difficulty with feeding, cough, weight loss, and fever.

Because of a high white blood cell count ( $30 \times 10^3/\mu\text{l}$ ), the diagnosis of pneumonia was made with a differential of neonatal sepsis. Other hemogram parameters and bloodwork up were within the normal range. The patient was put on antibiotics, with no improvement of symptoms. On the 12th day, with a newly discovered murmur on heart auscultation, tachycardia, and bounding pulses, an echocardiogram was performed, which showed features of patent ductus arteriosus (PDA) with a moderate-to-large left-to-right shunt. There were no additional cardiac malformations (such as coarctation or interrupted aortic arch or pulmonary atresia). The chest x-ray imaging was nonspecific for neonatal pneumonia. The infant was kept on oxygen; treatments with digoxin (1.5  $\mu\text{g}/\text{kg}/\text{d}$ ) and furosemide (1 mg/kg/dose) at 12-hour intervals were initiated. Intravenous fluid restriction at <130

mL/kg/d and parenteral nutrition were recommended. Indomethacin (0.1 mg/kg) was administered orally at 8-hour intervals. With the improvement of symptoms, the infant was discharged on the 38th day and followed up through the clinic as an outpatient.

The second patient was a 24-year-old primigravida admitted in labor at 32 weeks gestational age with cardiac-related complications. In the previous 2 years, she had been followed up at the cardiac clinic for rheumatic heart disease before pregnancy. Before and during pregnancy, she was on digoxin 0.125 mg twice per day and furosemide 20 mg twice daily, and monthly benzathine penicillin injection. She had been raped by her cousin, which had resulted in pregnancy. Her echocardiographic findings showed severe mitral stenosis and moderate aortic stenosis. She had a normal vaginal delivery of a female infant weighing 1600 grams with an Apgar score of 6 at 5 minutes.

The infant was admitted at NBU for prematurity and acute respiratory distress. On the 4th day following birth, the neonate developed jaundice, hypoxia and persistent respiratory distress. The infant was found to have a murmur on auscultation. Echocardiography was requested because of persistent cyanosis and respiratory distress, which showed features of a large ostium secundum atrial septal defect (ASDII) with a minuscule left-to-right shunt. There was increased hemoglobin (20 g/dl) and hematocrit (72%). Other blood work was normal. The infant was managed conservatively with oxygen supplementation, antibiotics, intravenous fluid and parenteral nutrition. With the improvement of symptoms, the infant was discharged after 55 days through the clinic as an outpatient.

## Discussion

Congenital heart defects are a global burden affecting 9.4/1000 of births [1]. In developed countries, access to healthcare and diagnostic technologies has substantially improved the reporting system for congenital heart disease (CHD). However, in many developing countries, there is a paucity of data on the birth prevalence of CHD. This is due to constrained diagnostic capability, poor health-related statistics, lack of birth-defect surveillance and

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registries and reliance on hospital-based rather than population-based studies [2]. In this study, the authors acknowledge these gaps.

Regarding the causes, multiple risk factors associated with CHDs have been studied, but in most cases, a cause-and-effect relationship has not been clearly established. These risk factors include genetics and environmental factors. Recently, consanguinity as a risk factor has been added to the list by different studies with similar conclusions. In this paper, we discuss each of them as obstetricians and gynecologists and as clinicians. Regarding genetic factors, familial forms of CHD have provided most of the genetic information on structural heart disease. Evidence has shown an association between the number of genes and CHDs [3]. These genes include NKX2-5, GATA4, TBX5, NOTCH1, and TBX20 [3]. To date, these studies have contributed to improving clinicians' understanding of both familial and sporadic forms of CHD.

Previous studies across the world have shown an association between environmental factors and CHDs. In the particular context of this study, the clinical risk factors are broadly discussed. According to Robert B. Hinton [4], the clinical risk factors for congenital heart defects include maternal health (age, prepregnancy BMI, type 1 diabetes status), maternal exposures (smoking, medications, chemicals), and complications of pregnancy (hypertension, infection, gestational diabetes). Advanced maternal age (AMA) is a known risk factor for CHDs. Moreover, evidence has shown that even in the absence of fetal chromosomal abnormalities, maternal age is still a risk factor for congenital heart defects. In line with this finding, Claire E. Schulkey et al [5] conducted a study on ovarian transplants between young and old mothers. The incidence of ventricular septal defects (VSDs) was significantly greater among the Nkx2-5+/- offspring of older mothers. The first case report was regarding a 38-year-old woman who gave birth to female infants with PDA. This may not be a permanent heart defect because PDA may complicate several neonatal disorders including prematurity and low birth weight, bronchopulmonary dysplasia (BPD), chronic lung disease (CLD), and necrotizing

enterocolitis (NEC) [6].

The improvement of the baby's symptoms after medical treatment confirms the hypothesis. Moreover, evidence has shown that even a neonate born at term, the ductus arteriosus can be closed within 2 to 3 days following birth. In addition, studies have established an association between increased maternal BMI, especially obesity and CHDs. However, the mechanism of association between obesity and birth defects is not clear because diabetes type 2, which is associated with obesity, does not increase the risk of CHDs. In a systematic review and meta-analysis conducted by Guang-ju Cai et al [7], obesity was found to increase the risk of any congenital heart defects (hypoplastic left heart syndrome, pulmonary valve stenosis, and outflow tract defects). However, underweight was not found to increase the risk of CHDs but did increase the risk of aortic valve stenosis in offspring [5].

In both cases, with normal or abnormal maternal weight, either underweight or overweight or obesity, the authors are in agreement that preconception maternal health and nutritional supplementation during pregnancy remain the most important factors to determine the risk of congenital heart defects. Moreover, evidence has shown that most risk factors of congenital heart defects or birth defects are preventable. In the first case, poor maternal nutritional health actually predisposes unborn infant to birth defects. The beneficial effects of preconception healthy nutrition and nutrient supplementation have been well established. To date, evidence has shown that preconception diets deficient in folate, for example, contribute to the development of several birth defects, including CHDs. Sylvia Alice Obermann-Borst [8] clarified the mechanisms underlying the beneficial effects of periconceptual folic acid, especially the one-carbon pathway, which is important in the periconceptual period for embryonic and placental development, in which B vitamins, including folate, serve as methyl donors, substrates and cofactors.

The author [Sylvia Alice] demonstrated that nutritional deficiencies particularly of folate, due to malnutrition, use of folate antagonists, metabolic

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derangements or polymorphisms in genes involved in the same pathway (methylenetetrahydrofolate reductase gene, MTHFR) in turn causes deranged synthesis of proteins, lipids, DNA and RNA, DNA repair mechanisms and DNA methylation. Tissue-specific derangements in DNA methylation may contribute to birth defects, including CHDs, and global derangements in DNA methylation, leading to impaired growth [8]. Similarly, van Driel LM et al [9] found that a deranged one-carbon pathway with high maternal concentrations of total homocysteine (tHcy) and S-adenosylhomocysteine (SAH) and a low S-adenosylmethionine (SAM): SAH ratio was significantly associated with an increased risk of having an infant with CHDs. Therefore, poor maternal nutrition is an important environmental risk factor for birth defects, including CHDs and growth restriction.

The maternal infection has been associated with an increased risk of CHDs in offspring. These include viral infection (such as infection with rubella or cytomegalovirus) and bacterial infections (such as syphilis). Regarding maternal RHD and CHDs in offspring, there is paucity of data. Rheumatic heart disease is one of the long-term complications of acute rheumatic fever. The latter [acute rheumatic fever] is caused by the group A streptococcus, which affects large proportion of people living in poverty [10]. In 2006, one study had hypothesized that maternal exposure to rheumatogenic groups of hemolytic-streptococcus may play a role in the pathogenesis of congenital heart disease in offspring. In his study, P. Eghtesady [11] believed that this could potentially be mediated by streptococcal-induced anti-cardiac myosin antibodies. To date, evidence has shown that anti-cardiac myosin autoantibodies are linked to several autoimmune diseases of the heart, including autoimmune myocarditis and rheumatic carditis, the most serious manifestation of group A streptococcal induced rheumatic fever [11]. Although the relationship between maternal exposure to rheumatogenic groups of hemolytic-streptococcus and hypoplastic left heart syndrome (HLHS) has been established, maternal RHD has not been reported as risk factors of heart defects in offspring. Therefore, further studies with large number of participants are

needed to establish such relationship. In addition, maternal medication during pregnancy has been severally reported as an important risk factor of CHDs. These include antibiotics (nitrofurantoin, trimethoprim-sulfamethaxole, cephalosporin and quinolone [used before 7 weeks of gestation]), antidepressants, and antiepileptics among others. In this study, drugs prescribed for the 2 patients seem not increase the risk of CHDs in offspring.

Regarding consanguinity, several studies have found that consanguineous parental marriage is associated with an increased risk of CHDs in children. For example, Faisal O. Alatawi [12] reported up to a 57% prevalence of congenital heart defects among infants born to consanguineous marriages in Saudi Arabia. Similarly, Deveshwar Dev et al [13] found that consanguinity in parental marriages confers an increased risk of CHDs in offspring. However, all these studies have not yet established the cause and effect relationship between consanguineous marriage and CHDs in offspring. In sub-Saharan Africa, consanguineous parental marriage is prohibited in most cultures. This may be a protective factor against CHDs in offspring. The second patient reported that she was raped by her cousin and became pregnant. Yunis K et al [14] found that first-cousin marriage was a significant risk factor for ventricular septal defect (VSD), atrial septal defect (ASD), hypoplastic left heart (HLH), and single ventricle (SV). From the extensive reading, secundum ASD can be caused by genetic and nongenetic syndromes. Genetic syndromes include Down, Holt-Oram, and Noonan syndromes [15, 16]. Nongenetic ASDII, like other nongenetic CHDs, is known as sporadic CHDs [16, 17]. In this case, despite the lack of genetic tests from the rapist, family history guided the classification of the case as nongenetic in origin.

To date, the introduction of a conventional approach for the prenatal diagnosis of congenital heart defects has accurately increased the detection of CHDs. Two-, three- and four-dimensional (known as 2D, 3D, and 4D) fetal echocardiography or fetal magnetic resonance (MRI) imaging are actually used with a unique purpose to improve the prenatal diagnosis of CHDs or birth defects [18]. This advanced technology

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is out of reach of most affected patients in resource-limited settings. In addition, the introduction of multidisciplinary care and new technologies dedicated to the management of patients with cardiac disease have contributed to reducing mortality and morbidity among affected neonates [3]. Centers offering both diagnosis and treatment for neonates with complex CHDs are financially and geographically out of reach of most affected families in developing areas. The burden placed on the child, family, society, health care institutions and insurance companies is also enormous. The 2 patients survived because they suffered from noncomplex CHDs; however, their conditions remained a burden on the family.

### Conclusion

Congenital heart defects have a multifactorial origin, with contributions from genetic and environmental factors. The risk of CHDs in offspring varies with the maternal strain background. In the context of this study, maternal health (age, prepregnancy BMI or nutritional status) and neonate factors (prematurity and low birth weight) in the first case and consanguinity in the second case were identified as potential risk factors for CHDs in offspring. We acknowledge the efficacy of preconception nutrient supplementation and healthy nutrition during pregnancy for preventing CHDs. In addition, it is difficult to conclude that maternal rheumatic heart disease is a risk factor for CHDs in offspring; however, further studies are needed to interrogate the current findings.

### Ethics approval and consent to participate

We obtained formal approval from Moi University-Moi Teaching and Referral Hospital Institutional Research and Ethics Committee (IREC).

### Consent to publish

Written informed consent for publication was sought from the patient and IREC.

### Availability of data and materials

We used our own materials and data.

### Competing interests

The authors declare that they have no competing interests.

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The study was entirely supported through scholarship.

### Author contributions

Philippe A. Poli is the principal investigator who conducts the study and writes the manuscript draft. Orang'o E. Omonge and Felix A. Barasa participate to the conception of the study, guide in the manuscript writing and scientific contribution.

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