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Case Report
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Mitral Endocarditis in Early Pregnancy: Case Report and Mini-Review

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Abstract

Background: Infective endocarditis in pregnancy is a rare but severe clinical condition, both for the mother and the foetus. Symptoms may be misleading due to their confusion with the expected effects of pregnancy.

Case Presentation: A 37-year-old woman, gravida 7 para 2, pregnant at 17 weeks of gestation was diagnosed with an infective endocarditis caused by *streptococcus mitis* after a persistent inflammatory syndrome with dry cough. Echocardiography confirmed mitral endocarditis after positive blood cultures, showing a moderate mitral insufficiency with vegetations. At 17 weeks of gestation, the patient underwent cardiac surgery under cardiopulmonary bypass. A successful mitral replacement was carried out without complications. At 22 weeks of gestation, ultrasound demonstrated a major cerebral malformation with hydrocephaly, and abnormal kidneys differentiation. After premature rupture of the membranes at 31 weeks and three days with antibiotics, the patient delivered a girl of 1840 grams, with an Apgar score of 9-8-8. The clinical exam of the baby showed a macrocephaly and a setting-sun sign. The baby died a few hours after delivery.

Conclusion: Treatment of infective endocarditis in pregnancy poses a dilemma due to the balance of risks for the mother and the foetus. As illustrated by our case, when endocarditis occurs early in the pregnancy, the necessary cardiac surgery requires the adoption of specific precautions. Despite these precautions allowing the foetus to survive surgery, severe malformations may lead to newborn's early death.

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Case Presentation

A 37-year-old patient, gravida 7 para 2 was hospitalized for an endocarditis at 17 weeks of gestation. Her medical history revealed 4 miscarriages, a C-section, one vaginal delivery birth and curettage. At 15 weeks of gestation, the patient was hospitalized for a suspicion of appendicitis with an inflammatory syndrome (CRP 80.8 mg/L and WBC 10.54 10^3/mm3), abdominal pain, nausea, vomiting and diarrhoea. The abdominal ultrasound revealed a sensible appendix of 6 mm (normal average is 5 mm) with some peritoneal liquid. The obstetrical exam was clear and reassuring with a foetal cardiac activity and the bacterial samples were negative. The patient was hospitalized and the clinical evolution cleared out the suspicion of appendicitis. Abdominal pain abated, leaving a sensitive epigastric discomfort. Gastroscopy showed moderate sign of gastroesophageal reflux an antacid was prescribed.

Control of biology the next day showed persistence of the inflammatory syndrome (CRP at 115 mg/L and WBC at 11.42 10^3/mm3) but a normal obstetrical and abdominal exam. The patient returned home with an appointment at the gynaecological outpatient clinic three days later. At this appointment, the patient was found unwell, describing extreme weakness and tiredness; she had some dry cough without rhinorrhea or respiratory distress. The blood test confirmed the inflammatory syndrome and showed anaemia (CRP 73.3 mg/L and WBC 8.84 10^3/mm3 and haemoglobin at 9.6 g/dl).

The patient was referred to an infectious disease specialist who found a clear clinical examination, including for signs of respiratory infection. Inflammatory syndrome was stable (CRP at 65.3 mg/L

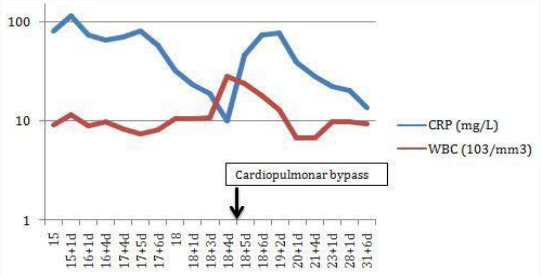

Figure 1: Laboratory investigations.

Figure 2: Anatomical view of the specimens of the resected leaflets.

and WBC 9.65 10^3/mm^3), serology for CMV and EBV presented acquired immunity (positive IgG), mycoplasma and chlamydia serology was negative. No antibiotics were given. One week later, at 17 weeks of gestation, the patient was only complaining of tiredness but presented with sub pyrexia at 37.7 ºC. RX thorax was negative.

The blood test showed persistence of inflammatory syndrome and anaemia (CRP 70.1 mg/L and WBC 8.26 10^3/mm3; Hb 9.1 g/dl); urine samples and vaginal smears were negative. Blood cultures were positive for Gram-positive cocci in chains. A cardiac ultrasound confirmed an infective endocarditis and Penicillin G 5 million units six times a day was started. Twenty-four hours later, the blood test culture confirmed the presence of Streptococcus mitis. The trans-oesophageal ultrasound describes a mitral endocarditis, probably on both sides of the mitral leaflet with a secondary moderate mitral insufficiency and some degree of valvular destruction. The vegetations were measured at 13 mm to 15 mm. The other valves were clean. The left heart function was conserved (Left Ventricular Ejection Fraction (LVEF) was 60 %) and the left ventricle was not dilated.

The antibio therapy was set at Penicillin G 3 million units six times a day. The usual oral origin of *streptococcus mitis* led to a suspicion of dental infection. The patient had teeth repair 3 months earlier and the dental exam confirmed an osteitis at the level of the 24th teeth and caries on the 27th. The 24th was extracted a few days later.

To exclude potential complications of the endocarditis, a cerebral MRI was performed; it showed multiple foci of abnormal signal at the level of the right paramedian protuberance, the left cerebellar hemisphere and the left thalamic capsule. Those brain lesions had no clinical repercussion. A duplex scan of the bloods vessels of the neck was normal, showing neither plaque nor mycotic aneurysm. At this time of the pregnancy, the ultrasound showed a foetal heartbeat, movements and no sign of foetal distress or complications. After 48hours of antibiotics, blood cultures became negative and the inflammatory syndrome was improving (CRP 58.1 mg/L and WBC 8 10^3/mm3) (Figure 1).

During a multidisciplinary discussion between cardiologists, obstetricians, infectious disease specialists and cardiac surgeons,

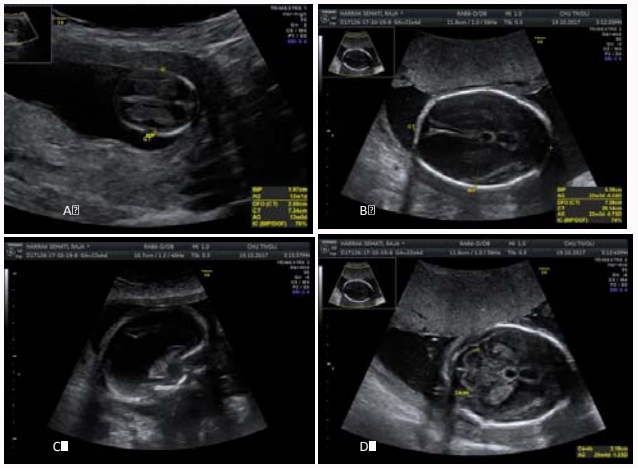

Figure 3: Ultrasound showing hydrocephaly and presence of cerebellum and brainstem structures.

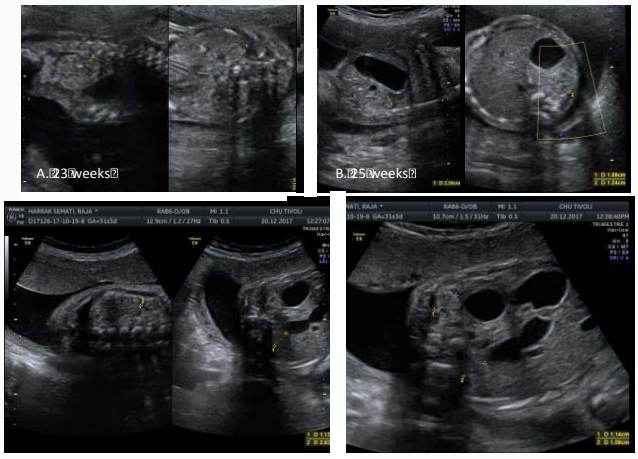

Figure 4: Kidney atrophy at different stages of the pregnancy.

it was decided to propose a mitral valve replacement. This decision emerged in order to cope with the increasing risk of embolisms and heart deficiency in the presence of a high suspicion of mitral valve destruction. A cardiac surgery under cardiopulmonary bypass was therefore planned at 18 weeks of gestation. The cardiac surgery lasted two hours, the cardiopulmonary bypass 1 hr and 27 min with 55 min of aortic clamp. The patient was positioned with a pillow under the right hip and monitored with ASA standard monitors, cerebral oximeter (INVOS) and a radial A-line.

In accordance with the obstetric team decisions, no specific foetal monitoring was placed considering the early onset of pregnancy but indomethacin was administered just before surgery to prevent contractions.

After the right atrium incision, the visualisation of the mitral valve revealed, as suspected, vegetations on both sides of the leaflet. The damaged valve was resected successfully (Figure 2) and a biological prosthesis was installed (Carpentier-Edwards Magna Ease, 27 mm).

The post-operatory period was unremarkable; the patient was extubated 6 hr after the end of the surgery. The foetal ultrasound showed a foetal heartbeat; reduced foetal movement were attributable to the anaesthetic drugs given during the surgery. The patient left the

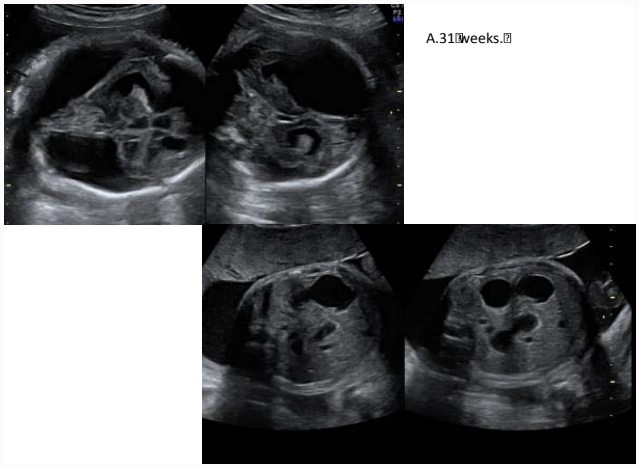

Figure 5: Ultrasound follow-up. The remaining cortex in the frontal lobe and the intestinal dilatations.

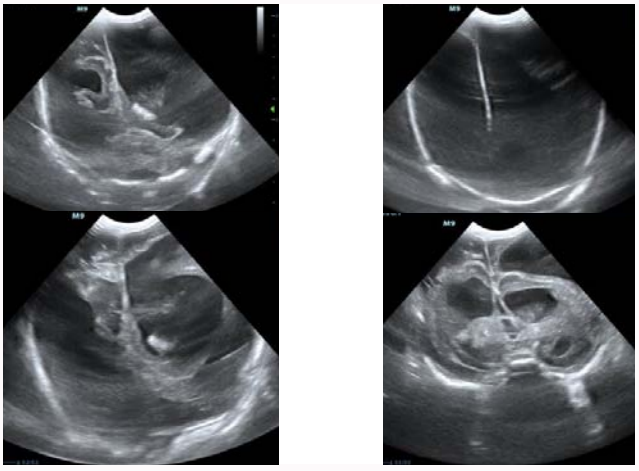

Figure 6: Ultrasound after birth with confirmed hydrocephaly with major cerebral malformations.

ICU after 48 hr and was transferred to the cardiac surgery ward.

The bacterial results of the mitral valve were negative. The cardiac ultrasound performed 5 days after surgery indicated normal left and right functions, (LVEF >60%), without any hypertrophy or dilatation on both sides. The prosthetic valve was functional. A week later, the ultrasound showed a status quo with no sign of vegetation.

Clinically, the patient recovered progressively and the inflammatory markers returned within the normal range.

On the obstetrical side, frequent ultrasounds and obstetrician visits were organized during the hospital stay of the patient, revealing no sign of maternal or foetal disturbances. An outpatient visit at 19 weeks was reassuring with normal foetal heartbeat and movements. Still, the patient complained about more uncomfortable contractions and the cervix was shortening at 20 mm to 21 mm with no funnel. A treatment by oral progesterone 200 mg three times a day was started.

At 22 weeks, the morphological ultrasound revealed major cerebral malformation, hydrocephaly, and abnormal kidneys differentiation (Figure 3). The foetal growth was normal (percentile 50) and the amniotic liquid quantity was normal. The option of a medical termination of pregnancy was proposed to the parents who refused

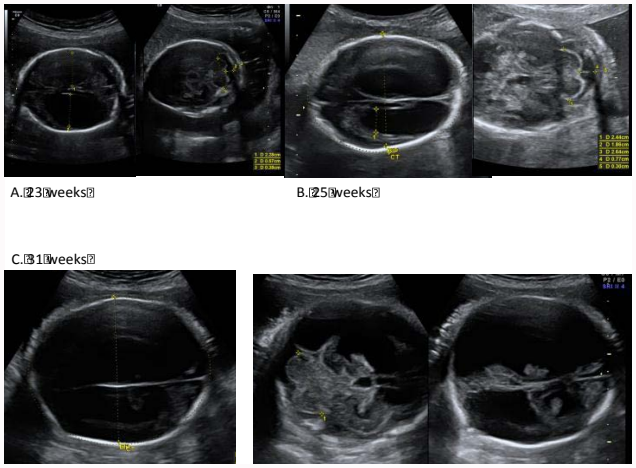

Figure 7: Hydrocephaly at different stages of the pregnancy.

it. At 31 weeks of gestation, the foetal growth was disharmonious; the cephalic parameters were expanding (p95), the femur growth was slowing down (p5) and the abdominal circumference was stable (p30). The hydrocephaly was worsened. On the temporal and occipital lobe, there was a total absence of cerebral tissue (Figure 4); it remained some on the frontal lobe (Figure 5).

The kidneys were atrophic without any differentiation (Figure 4). On the digestive side, there was a large stomach with intestinal dilatations, attributed to a digestive stenosis (Figure 5).

At $31^{6/7}$ weeks of gestation, the patient presented a Premature Rupture of the Membranes (PROM). After three days with antibiotics, the patient went into labour spontaneously and she delivered a girl of 1840 grams (P25-50), with a height of 42.9 cm (P51-75) and an Apgar score of 9-8-8.

The clinical exam of the baby showed a macrocephaly (the head perimeter measured 31.5 cm; P75-90) with a diastasis of the sutures and the bregma fontanelle was full and extremely large. The rest of the morphological and clinical exam was normal except for a global axial and peripheral hypotonia. On the neurological side, she presented a setting-sun sign attributed to hydrocephalus with raised Intracranial Pressure (ICP). The cerebral ultrasound at birth confirmed the major hydrocephaly associated with major destruction of the cerebral structures (Figure 6 and 7).

The baby died a few hours later.

Discussion

Infective endocarditis in pregnancy is extremely rare with an overall incidence of 1 in 100,000 pregnancies [1]. The pathogenesis of infective endocarditis involves the adherence of bacteria to damaged valves, and the organisms most frequently responsible for infective endocarditis are *Staphylococcus aureus*, *Streptococcus species* and *enterococci*, which cumulatively are responsible for 80% of the cases [1].

The patients at risk are Intravenous Drug Users (IVDU), representing up to 14% of the cases [2], prosthetic valve owners and patients with previous history of congenital heart disease or infective endocarditis. During pregnancy, infective endocarditis bears a high maternal and fetal mortality (rate ranges from 19.4% to 33%, and 15% to 29%, respectively); it is therefore difficult to manage since the risks

of any intervention need to be balanced between the two lives [1,3-5].

The patient here described developed an infective endocarditis due to *Streptoccous mitis* after a tooth repair; in the literature other cases have been caused by minimal surgery such as wedge excision for paronychia in which *Staphylococcus lugdunensis* was the pathogen [6]. Right-sided infective endocarditis are more common in intravenous drug users and *Staphylococcus aureus* is then the most preponderant pathogen [2].

In two cases reported in the literature, infective endocarditis developed in the presence of a congenital heart abnormality. This was a minor congenital ventricular septal defect in one case and a mitral prolapse in the other and the pathogens were *Staphylococcus lugdunensis* and *Streptococcus species* [1,7].

Symptoms of infective endocarditis during pregnancy are often difficult to recognize because there are confused for those of a normal pregnancy. Tiredness, tachycardia, slight dyspnoea or intestinal pain as in our patient, do not raise suspicion of cardiac dysfunction in this condition. The main symptoms reported in the literature, such as fever [5,6], dyspnoea or tachypnoea [2] actually orient towards diseases that are far more frequent during pregnancy, such as thrombotic embolism, pleural effusion or pneumonia. The minor symptoms often reported, such as tiredness and "unwell" feeling [1,7] do not draw the attention of the clinician towards the right diagnosis either.

Severe endocarditis can cause septic embolism events. Left-sided lesions provoke systemic emboli and cause neurological, cutaneous, vascular peripheral thrombosis lesions or renal dysfunction [1,2,5]. Right-sided valvular vegetations are causing pulmonary emboli leading to respiratory distress, tachycardia, low oxygen saturation and chest pain [2]. Most of the cases reported showed abnormal laboratory tests with leucocytosis, inflammatory syndrome with elevated C-reactive protein and anaemia. Blood samples were generally positive within 48 hours for the presence of bacteria in the cases reported and the pathogen belonged to the Streptococcus or *Staphylococcus species*. The echocardiogram mostly described vegetations, but are also reported destructed valves, abscess, regurgitations or stenosis on either right- or left-side heart; lesions on both sides are reported too [2].

Of notice, the Modified Duke Criteria used to establish the diagnosis of infective endocarditis based on a computation of major and minor criteria are meant to be applied without any adaptation in pregnant women.

The major cardiac complication of infective endocarditis is congestive heart failure occurring in 50%-60% of cases. Other complications include perivalvular extension leading to abscesses, fistulas and pseudoaneurysms. The most frequent and most severe extra cardiac complication is cerebral septic embolism [6]. Systemic emboli occurs in 22% to 50% of pregnant patients with infective endocarditis [1], the risk is increased in the presence of large, mobile vegetations, in particular in mitral position [6]. Of notice, our case accumulated all risks factors for systemic emboli. It was therefore not surprising that brain MRI revealed multiple sites of cerebral emboli in our patient: fortunately, locations and sizes of the cerebral emboli did not led to neurological deficits. Pregnancy obviously raises specific issues when it comes to the surgical treatment of infective endocarditis-related valvular deterioration. Cardiopulmonary Bypass (CPB) is required for such surgical procedures and it may impact foetal haemodynamic condition. CPB was first used in a pregnant woman in 1959. Since then, improvements were proposed to reduce as much as possible maternal and foetal morbidity and mortality during CPB. This resulted in a maternal mortality around 3% for CPB performed during pregnancy, a figure similar to that for non-pregnant patients.

On the other hand, risk for the foetus remains an important concern. In the literature, foetal morbidity and mortality during maternal cardiac surgery reached figures as high as 9 and 16% to 30%, respectively; for what concerned the risk of foetal demise, it was higher before 15 weeks of gestation [8-10]. Yuan et al. [8] reviewed 155 cases of CPB during pregnancy described in the literature between 1991 and 2013, infective endocarditis was the indication of CPB in 7.7% of the cases and the main indication was a valvular disorder of another cause (37%). For what concerned the foeto-neonatal outcomes, there were 4.5% spontaneous abortion, 4% stillborn and 3% of termination of pregnancy; the global foeto-neonatal mortality rate was 18,6%. This review concluded that the onset of cardiac symptoms followed by cardiac surgery with CPB during the early period of pregnancy led to higher foeto-neonatal mortality rates than in later periods. In fact, foeto-neonatal mortality rates progressively decreased from the first through the third trimesters. Foetal demise was actually often associated with premature delivery.

Considering the risk for the foetus outcome, it is preconized to favour a c-section before CPB when pregnancy is sufficiently advanced. In a review covering twenty years, almost half of the patients (43%) had c-section before CPB [9], in the other largest review, the rate was 41.9% [8]. Two reasons justify the practice of a c-section before CPB in the second and third trimester. First, for children born after the 28th week, the current risks linked to prematurity are much lower than previously, thanks to the advances in neonatal care. Second, foetal mortality is higher in the third trimester after emergency surgery [10].

When a CPB is performed during pregnancy, some cardiac and anaesthetic conditions need to be taken into consideration; many studies have shown that pump flow and mean arterial pressure are the most important factors influencing foetal oxygenation [10,11].

In experimental CPB, the placenta blood flow is significantly higher when the flow is pulsatile [10]. Pulsatility prevents low perfusion and limits the rise of vascular resistance. To overcome elevation of resistance, improve placenta blood flow and prevent acidosis, vasodilators can be used. Uterine contractions are described as an important factor of placenta blood flow reduction provoking foetal bradycardia. Tocolytics are highly advocated and used to prevent this situation in advanced pregnancy when these effects of uterine contractions are obviously more frequent [10].

Cardioplegia for cardiac surgery has also been suspected to cause foetal demise, since it may increase serum potassium levels, especially in cases of prolonged period of cardioplegic arrest. Maternal hyperkalemia increases potassium into the foetal circulation and leads to conduction disturbances that may ultimately result in foetal cardiac arrest. The literature advises to monitor serum potassium concentration, aiming at maintaining concentration <5 mmol/L [9,10,12]. In our case, following this recommendation, we monitored potassium concentration during CPB and the maximum potassium concentration recorded in the blood was 5.12 mEq/l. Acidosis was also monitored with a maximum pH decrease set at 7.29.

We also followed other precautions that are mentioned in the literature, to reduce foetal risks. The main precautions are to minimize CPB time, to keep a normothermic stage, to maintain a

high flow rate (> 2.4 L/min/m^2) and a mean arterial pressure >70-75 mmHg [9-12]. In our case, CPB time was 87 min and aortic cross clamping time was 55 min; the flow was targeted above 3 L/min/m^2; the systemic mean arterial pressure was kept between 70 and 85 mmHg and systemic normothermia (36.5°C to 37°C) was achieved during the whole procedure. Additional strategies include minimizing blood loss, controlling uterine displacement to avoid aortocaval compression (at least >20 weeks of gestation), optimizing maternal oxygen saturation, keeping hematocrit in the normal range and avoiding maternal hypoglycaemia [9-12]. To keep hematocrit >27%, our patient received three blood units to compensate a blood loss of 260 ml, which is close to the median in the literature [8].

In the Mayo Clinic Review (of 1976 to 2009) [9], 21 cases were analysed and none of the foetus or newborn presented malformations, although complications occurred in premature infants, including intrauterine growth restriction, respiratory distress syndrome and prolonged hospital stay. Long-term data revealed a developmental delay in preterm born infants for seven of them. In our case, the foetus developed major cerebral malformations, which are not frequent consequences of infective endocarditis during pregnancy. In the review by Yuan, a case report of 1996 was mentioned in which the foetus showed, two days after cardiac surgery, an hydrocephalus associated to hydrops [8,13]. In that case, CPB was performed at 19 weeks of gestation for an aortic valve replacement; CPB conditions were adapted to pregnancy except for a non-pulsatile perfusion (mean arterial pressure was 77-90 mmHg, peak flow rate was 3.5-4.0 L/min/m2 and core temperature was 34-35°C).

In the review of the literature by Pomini [12], one case which occurred in 1983 was complicated by a hydrocephaly at 18 weeks, after CPB for a mitral valve replacement at 6weeks of gestation [14]. In that case, the patient received a prosthetic valve and presented with thromboembolic complications. The same review mentioned two cases from the same article in which foeto-neonatal malformations occurred, but no details are provided about their nature. In one case, surgery was performed at 15 weeks and the mother delivered at 36 weeks; in the second case, the mother was operated at 20 weeks for a ventricular septal defect and she delivered at term. In this same cohort, there was also one case of stillbirth at term after surgery at 17 weeks [15]. Of course, the prenatal screening with ultrasound was not as precise as today in these various cases reported.

When the decision has been taken that the cardiac condition of the patient imposes a surgical procedure, a second decision arises: when should we proceed? To decide on the best timing appears a challenging task and the literature does not provide non equivocal guidelines to set this decision. Therefore it needs to be taken on a case by case basis, taking into account the ethical dimension of the choice to be made. Indeed, early CBP will increase the risk of foetal demise, while delayed surgery will increase maternal risks [9]. This choice is complicated by the fact that, depending on the conditions and the priorities that have been established, one option may be to deliver the baby prior surgery. When this option is chosen, a new balance of risks appears since surgery is defer until later pregnancy, at a time that should theoretically ensure acceptable prematurity without taking too much risks for the mother [8]. This option obviously bears the risk of acute cardiac or cardio-embolic complications during the "stand-still" period.

Conclusion

Infective endocarditis in pregnancy is a rare but severe clinical condition, both for the mother and the foetus.

As illustrated by our case, symptoms may be misleading due to their confusion with the expected effects of pregnancy. Treatment poses a dilemma due to the balance of risks for the mother and the foetus. The condition requires in most cases a valve replacement with CPB and the clinician will tend to delay the procedure until a C-section may be safely organized before surgery. In our case, as in a few other cases previously reported, infective endocarditis occurred early in the pregnancy, imposing to expose the foetus to the risk of the therapeutic procedure. The foetus survived the surgery but, despite the adoption of precautions suggested in the literature, severe malformations led to the newborn's death a few hours after delivery.

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