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SHORT COMMUNICATION

IN UTERO CONGESTIVE HEART FAILURE DUE TO MATERNAL INDOMETHACIN TREATMENT FOR POLYHYDRAMNIOS AND PREMATURE LABOUR IN A FETUS WITH ANTENATAL CLOSURE OF THE FORAMEN OVALE

REUWEN ACHIRON*, SHLOMO LIPITZ*, DEBORA KIDRON§, MICHAEL BERANT‡, JULIUS HEGESH† AND ZEEV ROTSTEIN†

**Department of Obstetrics and Gynecology and †Pediatric Cardiology Unit, The Chaim Sheba Medical Center, Tel Hashomer and Sackler School of Medicine, Tel Aviv University; ‡Pediatric Cardiology Unit, Beilinson Medical Center; §Department of Pathology, Sapir Medical Center, Israel*

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SUMMARY

A case of severe fetal congestive heart failure due to occlusion of the ductus arteriosus in a mother treated with indomethacin for polyhydramnios and premature contractions is described. Closure of the fetal foramen ovale that escaped detection by prenatal echocardiography was later demonstrated at neonatal autopsy. This case suggests that indomethacin treatment in a ductus-dependent fetus may be hazardous. Therefore, careful surveillance of the fetus exposed to indomethacin *in utero* is warranted.

KEY WORDS: maternal indomethacin; fetal heart failure; ductus arteriosus; foramen ovale

INTRODUCTION

In obstetrics, indomethacin, a potent inhibitor of prostaglandin synthetase, is recommended for two indications: (1) as a tocolytic agent (Niebyl *et al.*, 1980) and (2) to reduce polyhydramnios (Cabrol *et al.*, 1987). Indomethacin crosses the placenta freely and can inhibit the synthesis of prostaglandins in various fetal tissues (Moise *et al.*, 1990). The most serious side-effect reported with *in utero* exposure to indomethacin is premature constriction of the ductus arteriosus (Moise *et al.*, 1988). Other neonatal complications related to maternal indomethacin use are necrotizing enterocolitis and intracranial haemorrhage (Norton *et al.*, 1993).

Although the aforementioned adverse side-effects have been reported with indomethacin, recent reviews still recommend its use for the above indications (Morales *et al.*, 1989; Goldenberg *et al.*, 1989). We report a case with a characteristic syndrome comprising premature closure of the ductus arteriosus, congestive right heart failure, and myocardial ischaemic necrosis in a fetus with undetected closure of the foramen ovale. The mother underwent short-term tocolysis with indomethacin for premature contractions and idiopathic polyhydramnios.

Addressee for correspondence: R. Achiron, MD, Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center, Tel Hashomer 52621, Israel.

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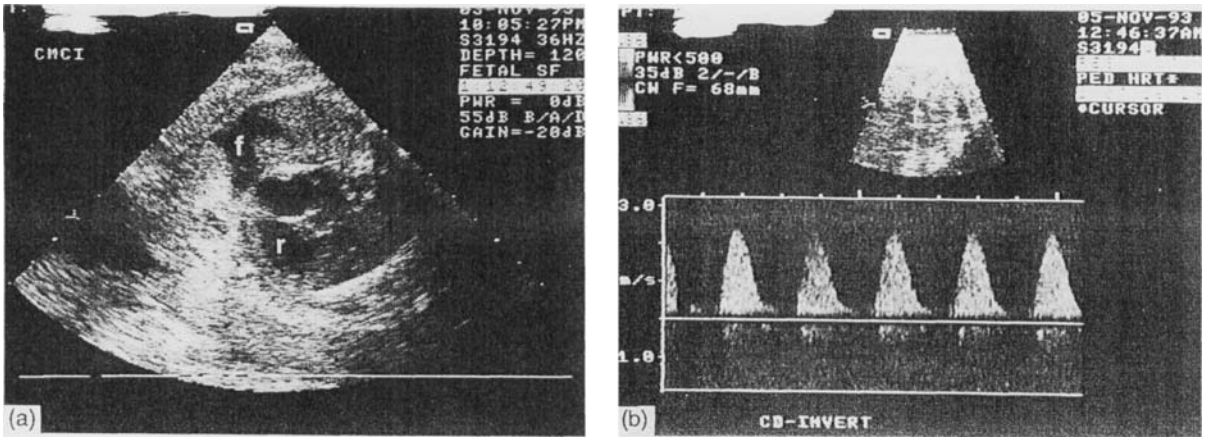

Fig. 1—Prenatal ultrasonographic findings: (A) short axis view of the fetal chest showing an enlarged akinetic right ventricle (r) and pleural effusion (f); (B) Doppler wave form from the ductus 2 days after the last dose of indomethacin. A high systolic velocity of 2·6 m/s was recorded

CASE REPORT

A 32-year-old gravida 1, para 0 underwent routine prenatal ultrasonography at 26 weeks' gestation. The patient had no previous medical complications and there was no family history of congenital anomalies or diabetes. At 17 weeks' gestation, amniocentesis (due to personal request) revealed a normal female karyotype. Routine ultrasonographic examination at 26 weeks confirmed mild polyhydramnios with fetal biometry corresponding to 26–27 gestational weeks. No gross fetal abnormalities or hydropic changes were noted. Fetal heart evaluation revealed a minimal difference in ventricle size and outflow: the right ventricle was larger than the left, and its myocardial wall and septum appeared to be thicker. In the light of these findings, diabetic cardiac myopathy was suspected. However, a normal glucose tolerance test and normal formal fetal colour Doppler echocardiography ruled out the above clinical diagnosis. At 30 weeks' gestation, premature contractions appeared and the patient was admitted to hospital. Because of the idiopathic hydramnios and premature contractions, indomethacin treatment, 250 mg, four times a day, was started orally. This regime was planned for 1 week. However, on the fifth day of indomethacin administration, a routine non-stress test recorded variable decelerations and a fetal biophysical score was therefore performed. Upper body soft tissue oedema with scalp oedema and significant pericardial and pleural effusions were evident. The right atrium and ventricle appeared enlarged and the right ventricle seemed akinetic (Fig. 1A). No ductal flow or tricuspid regurgitation could be detected by colour Doppler flow. Ductal occlusion due to indomethacin and severe right heart failure was diagnosed.

Indomethacin was withdrawn and repeat fetal echocardiography 2 days later demonstrated improved contraction of the right ventricle, with a high systolic velocity of 2·6 m/s through the ductus arteriosus (Fig. 1B). Despite this, pleural effusion with upper body skin oedema persisted. Because of the possible anoxic effect on the right ventricle, the patient asked for medical termination of the pregnancy, which was performed with intracardiac potassium chloride injection. Pathological examination confirmed a thick, right ventricle and total occlusion of the foramen ovale with a narrow ductus. On microscopy, foci of papillary muscle necrosis with calcifications were also noted (Fig. 2).

DISCUSSION

In the present case, an association between prenatal use of indomethacin and severe *in utero* congestive right heart failure has been demonstrated. Although indomethacin is considered a safe tocolytic agent and has been used since the mid-1970s, it can cause fetal constriction of the ductus arteriosus (Moise *et al.*, 1988; Norton *et al.*, 1993). However, this was found to be transitory and no severe short- or long-term cardiac sequelae have been reported (Dudley and Hardie, 1985; Niebyl and Witter, 1986).

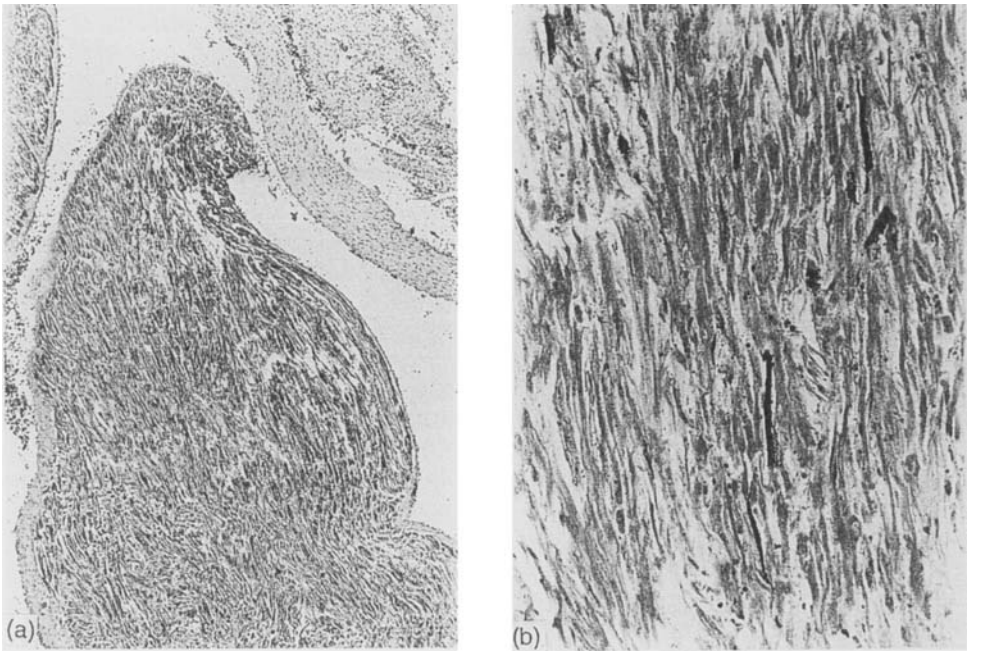

Fig. 2—Microscopic examination of the papillary muscle of the right ventricle shows (A) calcifications in isolated cardiac myocytes (H&E, × 40) and (B) ischaemic autolysis of the papillary muscle (H&E, × 400)

On reviewing the English literature, we were able to find only two anecdotal case reports describing the development of congestive heart failure secondary to maternal indomethacin ingestion in a twin pregnancy (Mogilner *et al.*, 1982). In the first case, it was postulated that the premature closure of the ductus arteriosus in one of the twins caused the hydrops fetalis. In the second case report, Hallak *et al.* (1991) described right ventricular hypokinesia and dilatation of both the right ventricle and the aorta, with tricuspid regurgitation, but without hydrops fetalis. It is of interest why, in the first case, the co-twin, who was exposed similarly to the same drug, did not develop cardiac failure and, in the second case, only one of the twins occluded its ductus arteriosus. Since indomethacin is used internationally, and in only two cases has its deleterious effect on the fetal heart been described, it can be speculated that a predisposing factor to such an effect should be present. In our case, the unexpected finding of a sealed foramen ovale diagnosed only at autopsy may explain why the fetal condition deteriorated after maternal indomethacin ingestion. In late gestation, about one half of the blood that reaches the right atrium normally passes to the left atrium through the foramen ovale. When this flow is reduced by premature narrowing of the foramen ovale, the diverted blood presumably passes into the right ventricle, increasing the output of that chamber. From this point, blood must pass through the still patent ductus arteriosus. In our case, with colour Doppler echocardiography it was not possible to show any flow through the ductus arteriosus, but on withdrawal of the drug some flow appeared, confirmed the transitory effect of indomethacin on the ductus closure.

However, since the ductus was the only possible route for drainage of the right heart, it is not surprising that in our case its occlusion caused strangulation and papillary muscle necrosis. This effect of indomethacin has been previously described in an animal model (Levin *et al.*, 1979). The only problem that should be resolved in our case is why the closed foramen ovale escaped *in utero* diagnosis. Although premature narrowing or closure of the foramen ovale is an infrequent, but not rare, anomaly, we were unable to find much literature.

In 1963, Lev *et al.* (1963) reported ten cases where restriction of the foramen ovale was noted at autopsy, and reviewed an additional 25 cases reported previously. Most of these had clinical features of hypoplastic left heart syndrome. In

1964, Naeye and Blanc reported 12 cases with premature closure or narrowing of the foramen ovale that were demonstrated at autopsy, ten of which had left heart chambers of normal or near-normal size. The authors explained that in these cases late closure of the foramen ovale resulted in normal development of the left atrium and ventricle and concluded that the left heart may not be hypoplastic, as has been assumed previously in cases with premature closure of the foramen ovale. Prenatal diagnosis of *in utero* constriction of the foramen ovale has been reported only twice. Hansmann and Redel (1982) reported two cases, both with hydrothorax. However, additional information on the chamber size is lacking. Fraser *et al.* (1989) reported a case in which the diagnosis was suspected *in utero* because of ballooning of the foramen ovale region into the left atrium. Both the left atrium and ventricle had normal dimensions. However, in this case, the diagnosis was not confirmed postnatally by cardiac catheterization. In the present case, the diagnosis of closed foramen ovale was made only postnatally and it escaped *in utero* diagnosis. Despite knowledge of the pathology at the time of reviewing the videotapes recorded prenatally, we were unable to recognize the constricted foramen ovale. The only possible hint for this abnormality that could be traced from the video was that the foramen ovale, instead of having a normal flapping motion, showed ballooning into the left atrium, with a clear colour noted to fill the aneuristic flap that reached the surface of the mitral valve. We hypothesized the following sequence of events in the pathophysiology of the present case. Narrowing of the foramen ovale led to the minimal difference in ventricle size and outflows, probably with secondary polyhydramnios. The time course is uncertain, but later closure of the foramen occurred and the fetus became ductus-dependent for draining the right heart. The constriction of the ductus by indomethacin treatment strangulated the only possible exit to the right ventricle, resulting in a dilated akinetic ventricle with secondary myocardial ischaemic necrosis. The appearance of upper body oedema may explain this congestive right heart failure.

Our case demonstrates that a careful evaluation of the fetal heart is needed in cases presenting idiopathic polyhydramnios. When anatomical abnormalities are absent, one should consider the possibility of premature narrowing of the foramen ovale, particularly when a minimal difference in ventricle size and outflow appears, and when the normal flapping motion of the foramen ovale is not demonstrated. We wish to draw attention to the possible toxicity of indomethacin in cases complicated by idiopathic polyhydramnios with preterm labour. In such cases, fetal echocardiography should be planned early after exposure, or the use of other tocolytic drugs should be considered.

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