CASE REPORT

FETAL WARFARIN SYNDROME
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ABSTRACT: A case is reported of a baby born with congenital abnormalities due to maternal ingestion of warfarin during pregnancy. Warfarin is known to be teratogenic, producing characteristic abnormalities, namely a hypoplastic nose, stippled epiphyses, and skeletal abnormalities. Cardiologists and obstetricians should also be aware of the possible teratogenic effects when considering warfarin therapy for a woman of childbearing age.¹

KEYWORDS: Warfarin Embryopathy, Depressed nasal bridge, Di Sala Syndrome.

INTRODUCTION: Fetal Warfarin Syndrome (that is. Warfarin Embryopathy) is a consequence of maternal ingestion of warfarin during pregnancy. Warfarin syndrome comprises a range of dysmorphology in the neonate with characteristic facial features.

MATERIALS AND METHODS: Here we present a case of a neonate whose mother was on unsupervised warfarin therapy during pregnancy. A brief review of literature is discussed. The treatment of symptoms in Fetal Warfarin Syndrome is symptomatic.

CASE PRESENTATION: Warfarin Embryopathy results as a consequence of maternal warfarin intake during the antenatal period. The manifestations are varied ranging from still births, abortions to dysmorphology and malformations of variable degree involving different organ systems. The disease is very rare and very few case have been reported internationally due to the alternative use of low molecular weight heparin in the first trimester during organogenesis and in the last week of gestation, also the reduced dosing of Warfarin and hence the incidence in India also.²

We have report on a neonate with classical history of maternal warfarin intake and classical features. Mrs. X the mother was apparently normal till four years ago when during her first pregnancy (first) at seven months of gestation the mother developed breathing difficulty and intense abdominal pain lasting for one to two days after which she was admitted in hospital and vaginal delivery was conducted, baby cried immediately after birth, further details not known. Baby was shifted to NICU in view of preterm and respiratory distress but there was no history of bluish discoloration of skin and mucus membranes nor was there any dysmorphology noted.

The baby died within a day and mother was unaware of the cause of death.

During the postnatal period the mother was evaluated and was diagnosed with a heart condition (mitral valve regurgitation) and was advised by doctors for cardiovascular surgery for the same after one year of medications, one of which was warfarin.

But after three months the mother conceived (second) again but had spontaneous abortion at one month of gestation.

In 2011 she successfully underwent surgery and was advised to continue medications of which one was warfarin.
One year after surgery she became pregnant again (third) and after one month of gestation she underwent spontaneous abortion.

During the present pregnancy (fourth) she was advised to stop warfarin totally by her obstetrician during one antenatal visit but irrespective of her advice she was always on irregular treatment with Warfarin and the mother herself is unaware of warfarin intake during the sixth to eight week. At thirty two weeks of gestation her family shifted to Bangalore for work purposes and at around thirty five weeks of gestation she developed premature rupture of membranes for which she was admitted in a local hospital but due to her significant history and fetal distress mother was referred to our hospital for further management. Here our cardiologist reduced the dose of warfarin to 2.5 mg.

The antenatal scans here shows absent nasal bone and stippled vertebrae (Fig: 1 & 2)

Baby was born by LSCS at thirty five weeks of gestation, indication being a precious baby, premature rupture of membranes of more than forty eight hours, maternal rheumatic heart disease and anemia. Baby had a very weak cry at birth, APGAR at 1 min 5/10 and 5 min 7/10.

In view of bradycardia and very weak cry, bag & mask ventilation was done with which there was significant improvement in vitals and it was slowly tapered after which baby had spontaneous breathing and active cry.

Baby had mild respiratory distress with intercostal recessions and acrocyanosis but no grunting. Thus in view of prematurity, bad obstetric history, mild respiratory distress and being a precious baby, the baby was shifted to NICU.

After admission to NICU, baby had mild respiratory distress with mild acrocyanosis and intercostal recessions HR: 145/min, RR: 70/min, PP: well felt, BP: 66/40 mmHg, SpO2: 90% at room air. Baby’s anthropometric measurements were: Weight – 1.9 kg, Length – 47cm, Head circumference – 31cm, Chest circumference –26cm

**Fig. 1: ANTENATAL USG – REVEALING ABSENT NASAL BONE**

**Fig. 2: ANTENATAL USG – REVEALING STIPPLING OF THE FETAL VERTEBRAE**
Fig. 3: 2D ECHO REVEALING THE-DILATED VENTRICLES

Fig. 4: 2D ECHO REVEALING PDA

Fig. 5: PHOTOGRAPH SHOWING THE DEPRESSED NASAL BRIDGE AND DYSMORPHIC FACIES

Fig. 6: PHOTOGRAPH SHOWING SHORT NECK

Fig. 7: SHOWS STIPPLED VERTEBRAE

Fig. 8 SHOWS STIPPLING IN LONG BONES
Baby was started nil per oral, nasogastric tube was inserted followed by chest x-ray to confirm positioning and in x-ray it was noted that the baby had a cardiomegaly and there were slight opacities in the lung fields mostly in the upper zone? congenital pneumonia (fig: 7). Hence in view of the cardiomegaly a screening ECHO was done which showed a patent ductus arteriosus of 3mm size and an ASD of 3mm size with mild enlargement of the LA & LV chambers. GRBS was monitored hourly, IV fluids were started, and antibiotics were started in view of premature rupture of membranes and chest x-ray findings and first day investigations were done. On day one baby continued to have mild respiratory distress and hypotonia and the respiratory rate was consistently around 60/min but baby was maintaining saturation well. ECHO done on day one showed an increasing size of the PDA to 3.5 mm. (Fig: 3 & 4)

Even by day two child continued to have mild respiratory distress and an ECHO screening showed the size to be 4 mm .In view of the increasing size of the PDA Ibuprofen was started on 10mg/kg on first day and then 5mg/kg on the subsequent two days. And the follow up scan reported the size reducing to 2.5mm on 4 and 1.5 on day 5 and on 0.5 mm by day six. And a follow up scan post discharge reported the PDA to be less than 0.5 mm. A whole body x-ray reported stippled vertebrae and pelvic bones. (Fig: 7, 8, 9)

In systemic examination, CVS examination showed a systolic murmur of grade 3/6 with all other systems within normal limits. Head to toe examination it was observed that the baby has depressed nasal bridge, a high arched palate, short neck.

Fig. 9: PHOTOGRAPHS OF X-RAYS SHOWING STIPPLING IN THE LONG BONES
Detailed laboratory evaluation was done. Ultrasound of brain and abdomen were normal. Computed tomographic imaging of the brain was planned but patient attenders wanted to take the baby against medical advice home due to financial constraints.

Ophthalmic evaluation was normal. Auditory evaluation of baby was not done as parents took the baby against medical advice due to financial constraint.

The baby had an apparently uneventful hospital stay. With the diagnosis of Warfarin Embryopathy the parents were counseled regarding the long term outcome and potential stigmata in the child.

**DISCUSSION:** Warfarin is a potential anticoagulant used in the management of a variety of thromboembolic conditions that depresses the synthesis of Vitamin K dependent clotting factors. It readily crosses the placenta because of its low molecular weight.

Warfarin is a relatively small molecule with molecular weight about 1,000 Daltons. Its unbound fraction easily crosses the human placental barrier to reach the fetal blood circulation. Since warfarin readily crosses the placenta, it is implicated in two major adverse effects.

First, it inhibits vitamin K recycling in the embryo resulting in hemorrhage in every fetal organ. Second, it interferes in vitamin K reductase activity which leads to a decrease in the production of vitamin K-dependent mineralization inhibitors in cartilage resulting in ectopic calcium deposits in epiphysis and nasal septum called epiphyseal stippling.

In addition, premature closure of growth plate and shortening extremities could ensue. Warfarin may inhibit arylsulfatase enzyme activity, the cause of X-linked recessive chondrodysplasia punctata, which has a phenotype identical to warfarin embryopathy.

Moreover, warfarin interferes in vitamin K epoxide reductase activity, which plays a role in the synthesis of some vitamin K-dependent proteins such as osteocalcin and Gla matrix protein, two essential components of bone and cartilage development.

In 1966, Di Sala reported the first case of fetal warfarin syndrome. Anomalies include nasal hypoplasia, choanal atresia, laryngeal abnormalities, and upper airway obstruction, and short neck, hypoplasia of distal phalanges, brachydactyly, and short limbs.

The most striking radiographic finding is pronounced epiphyseal stippling of vertebrae, sacrum and long bones during early childhood and disappears with age.

All the above results are from exposure to warfarin in the first trimester of pregnancy. Other teratogenic effects in fetuses exposed to warfarin after second or third trimester include optic atrophy, blindness, corneal opacity, deafness, microcephaly, hydrocephalus, epilepsy, Dandy-Walker malformation and mental retardation.

The greatest susceptible period for developing warfarin embryopathy is between the sixth to the ninth week of gestation.

Nasal hypoplasia and chondrodysplasia punctate are the two most consistent features of the syndrome.

Other common manifestations include cleft palate, cleft lip, choanal atresia or lip, CNS anomalies like hydrocephalus.

Bilobed lungs, coarctation of aorta, malformed ears and situs inversus have also been noted.
Following Prenatal Exposure from 6 to 9 Weeks.

Anomalies in the face seen are nasal hypoplasia and depressed nasal bridge, often with a deep groove between the alae nasi and nasal tip. And in the skeletal system the anomalies seen are stippling of uncalcified epiphyses, particularly of axial skeleton (vertebrae and pelvis), at the proximal femora and in the calcanei; stippling disappears after the first year.

Whereas hypoplastic distal phalanges that are shaped like inverted triangles with the apices pointing proximally are seen in the limbs.

Low birth weight; most demonstrate catch-up growth is usually noted in babies.

Occasionally seen are choanal atresia, cleft lip and palate, lung hypoplasia, severe rhizomelia; scoliosis; congenital heart defect; vertebral anomalies, asplenia, renal agenesis, hypospadias., structural defects of brain development.

Following Prenatal Exposure from fourteen to twenty weeks.

Microcephaly, hydrocephalus, Dandy-Walker malformation, agenesis of corpus callosum, midline cerebellar atrophy, seizures and spasticity, intellectual disability, speech difficulties are seen in the CNS system.

Whereas in the eye Optic atrophy, cataracts, microphthalmia, Peters anomaly can also be seen.

Other anomalies noted are intrauterine growth retardation, scoliosis, and tethered skin in the sacroccocygeal region.

The management is purely supportive depending upon the presentation of the child.

The prognosis of the children depends on the severity of the defects.

In immediate neonatal period airway management is essential. Those with hemorrhagic and CNS anomalies have poor outcomes. Long term effects are poorly understood.

Our case was diagnosed with Fetal Warfarin syndrome because of the significant warfarin intake history and the baby being Preterm, low birth weight, having the depressed nasal bridge, the short neck and the PDA and ASD and the stippled epiphysis on x-ray.

This case report should alert clinicians and, in particular, obstetricians to the teratogenic effects of warfarin and limit the use in first trimester & the last week of pregnancy and dosage to be limited to less than 5 mg so the severity of anomalies is reduced in the baby.

In contrast, in a recent retrospective multicenter survey, the Working Group on Valve Disease of the European Society of Cardiology concluded that heparin is neither effective nor safe for long-term use during pregnancy in patients with mechanical heart valves, bringing an increased risk of both thromboembolism and bleeding to mother and fetus.7

Any female patient in the child-bearing age who is taking warfarin should be warned against pregnancy. Furthermore, pediatricians should keep in mind for the possibility of the congenital warfarin syndrome in the newborn with the history of maternal warfarin usage, and can prevent the tragedy of an avoidable recurrence of birth defects in subsequent pregnancies.

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