J. Fetal Med. (December 2018) 5:233–236
https://doi.org/10.1007/s40556-018-0182-2

BRIEF COMMUNICATION

A Case of Coumarin Embryopathy After in Utero Exposure to Acenocoumarol

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Received: 15 April 2018 / Accepted: 9 July 2018 / Published online: 31 July 2018

Abstract Coumarins (warfarin, acenocoumarol, phenprocuomon) are well known agents that are prescribed for prevention of thromboembolic episodes in pregnant women who are on mechanical heart valves prosthesis. It acts as double edge sword as fetus is unnecessarily exposed to teratogenic effect of drug. Warfarin is well studied drug in terms of its tetratogenic dose, period of exposure, fetopathic effects. Acenocoumarol is well known teratogen but its effect and lethal dose on fetus is less reported. We report a neonate who was exposed to acenocoumarol throughout intra uterine life. Neonate showed all features of coumarin embryopathy (flat facial profile, depressed nasal bridge, short columella, skeletal stippling, short distal phalanges in hand) and cephalhaematoma in addition. We also summarised the clinical findings of all the cases reported so far of acenocoumarol embryopathy. Acenocoumarol has same teratogenic potential as of warfarin. Doses causing embryopathy remained unexplored field. Clinicians need to document properly so that scientific data can be generated as ethical issues arises in head to head trial of these drugs.

Keywords Acenocoumarol · Embryopathy · Chondrodysplasia · Calcification · Mid face hypoplasia

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Introduction

Oral anticoagulants are commonly prescribed drugs for prevention and treatment of thromboembolic phenomenon e.g. venous thromboembolism, acute coronary syndrome, and mechanical heart valves. Commonly used oral anticoagulants are Vitamin K antagonists (VKA) among which coumarin derivatives (warfarin, acenocoumarol,phenprocuomon etc.) are frequently used [1, 2]. In patients with artificial heart valves, the risk of thrombo-embolic phenomena increases dramatically during pregnancy due to the hypercoagulable state of gestation. In such patients, the efficacy of heparin has not been established and the oral anticoagulants (coumarin derivatives) are an effective option. But, dilemma with their use arises as they are known to cross the placenta [3]. Use of low molecular weight heparin (LMWH) is associated with maternal adverse effects like thrombocytopenia, alopecia, and osteoporosis. There is no generalized consensus on use of anticoagulant in pregnancy, but recent guidelines suggest either continuing oral anticoagulants or substituting them with subcutaneous LMWH in first trimester (6–12 weeks), then back to oral anticoagulants until close to delivery or taking LMWH or unfractionated heparin (UFH) throughout the pregnancy [4, 5]. No regimen is proved to be entirely safe for maternal use during pregnancy as there is a degree of risk both for mother and perinatal outcome with each regimen [6].

Oral anticoagulants are cheap, easy to administer and more effective than LMWH or UFH, but their use is associated with embryopathy and fetopathy and difficulty in maintaining stable international normalized ratio (INR) during pregnancy due to alteration of coagulation factor and natural anticoagulant levels owing to increase in plasma volume. Also, LMWH administration needs close

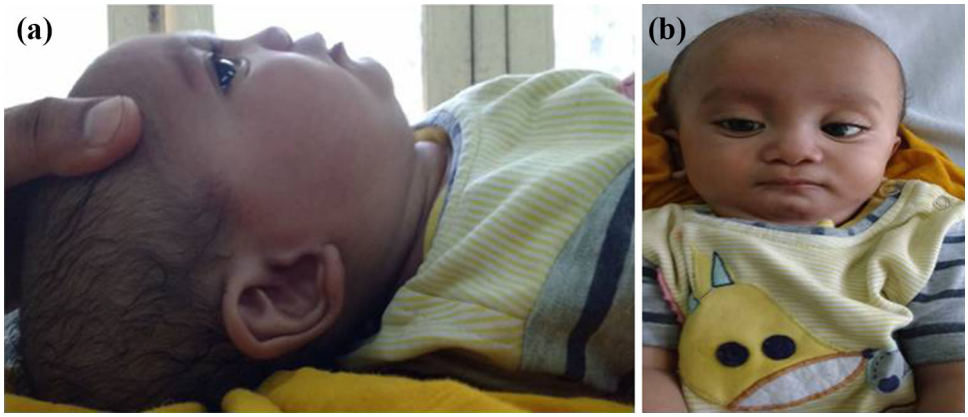

Fig. 1 **a**, **b** Facial profile of proband (frontal and lateral) showing nasal hypoplasia and short columella

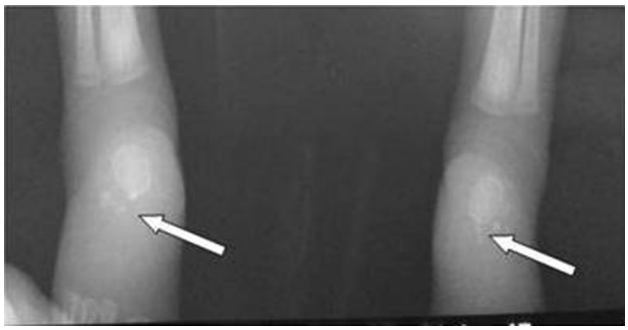

Fig. 2 X-ray of both calcaneum showing epiphyseal stippling

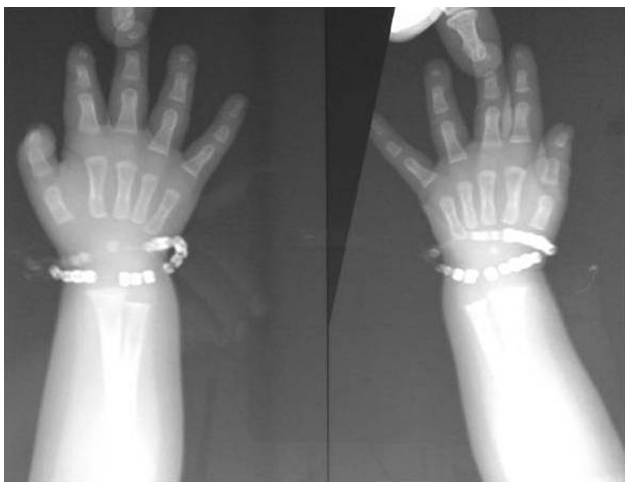

Fig. 3 Radiograph of bilateral hand showing distal phalangeal hypoplasia of right 2nd (2.5 mm; > 50% hypoplasia), 3rd (2 mm; > 60% hypoplasia), 4th (2.5 mm; > 50% hypoplasia and left 2nd (1.9 mm > 65% hypoplasia), 3rd (2.6 mm > 50% hypoplasia), 4th (2 mm > 65% hypoplasia)

monitoring of blood anti-factor Xa concentrations which are costly [4]. Prenatal exposure of coumarins affects the bone, cartilage, and the developing central nervous system [7].

Acenocoumarol has been reported to cause nose stippling, hydrocephalus, scoliosis, tethered skin in sacrococcygeal region, rhizomelia and intrauterine growth retardation (IUGR) [8]. This teratogenic interference occurs during the period of organogenesis. During early times, pathogenesis of the congenital anomalies found after in utero exposure to coumarin derivatives were thought to be based on prolongation of blood clotting time. It was also suggested that deformities in the child were caused by microhemorrhages and subsequent scarring and calcification [9]. Later on, new insights into pathogenesis suggest that Vitamin K-dependent proteins are required for development of bone, cartilage and developing central nervous system, these proteins are inhibited by oral anticoagulants [10].

Warfarin is well established teratogen with multiple case reports and case series highlighting its risk to developing fetus. We report a case of coumarin embryopathy after in utero exposure to acenocoumarol. We highlight its teratogenic complication and tabulate all the cases of acenocoumarol embropathy. We found seven more cases and tried to find prescribed dose, period of exposure, and perinatal outcome.

Case Report

A full term small for gestational age (SGA) baby was born to a primigravida mother by normal vaginal delivery, who was a known case of rheumatic heart disease (mitral regurgitation) operated with prosthetic valve replacement eight years back. Since then, mother was taking oral acenocoumarol (nicoumalone) thromboprophylaxis with a dose range of 3–4 mg daily. No history of any intrauterine fetal death. Antenatal period was uneventful with INR between 1.5 and 2.5. No LMWH prophylaxis was given during pregnancy. First and second trimester antenatal ultrasonography (USG) were normal, while third trimester USG showed polyhydramnios. Postnatal period was uneventful until day 24 of life when baby presented to us with nasal congestion, poor oral feeding. At admission,

Table 1 Congenital anomalies associated with in utero exposure to acenocoumarol

Authors	Daily dose	Exposure period (weeks)	Partus (weeks)	Nasal hypoplasia	Skeletal stippling	CNS	Others
Vanlaeys et al. [15]	–	0–26	Term	Yes	Yes	–	–
Weenik et al. 16]	–	13–38	40	Yes	–	–	–
Weenik et al. 16]	–	0–36		Yes	Yes	–	–
Lapiedra et al. [13]	–	0–6	22/elective abortion	–	–	Hydrocephalus/ scoliosis + tethered skin in sacrococcygeal region	–
De Vries et al. [17]	–	0–5 and 12–32	32	Yes	Yes	Hydrocephalus	IUGR, rhizomelia
Van Driel et al. [18]	–	8–12	41	Yes	–	–	–
Bony et al. [16]	–	Throughout pregnancy	41	Yes	Yes	–	Telebrachydactyly, cataract, bilateral pyeloureteral junction syndrome
Present study	3–4 mg/day	Throughout pregnancy	39	Yes	Yes	Cephalhaematoma over right parietal bone	Distal phalanx hypoplasia of bilateral 2nd, 3rd and 4th finger

baby was lethargic with hypoglycaemia. Baby had facial dysmorphology in form of flat facial profile, nasal hypoplasia, depressed nasal bridge (Fig. 1a, b at 6 months) and a firm swelling (approximately 2 × 3 cm) on right parietal prominence. Nasal length, measured from nasion to subnasale was 2.7 cm (between mean and − 1 sd score), normal philtrum (1.2 cm ∼ between mean and − 1 sd score), intercanthal distance (22 mm ∼ normal), short columella. Rest of systemic examination was normal. Her blood glucose level was low (35 mg/dl). Sepsis screen was negative. Radiologically, baby had epiphyseal stippling involving both calcaneum and talus bone (Fig. 2). Radiograph of bilateral hand showed hypoplasia of distal phalanges of bilateral 2nd, 3rd, and 4th fingers with variable degree of stippling (Fig. 3). Dermatoglyphics and fingernails are normal. Contrast-enhanced computed tomography (CECT) brain showed calcified cephalhematoma overlying the right parietal bone. Chest X-ray, USG abdomen, 2D-Echocardiography (ECHO) and karyotype were normal. We managed the baby with intravenous fluids, nasal saline drops and antibiotics. After 7 days of hospital stay, baby was discharged with proper feeding establishment and a plan to follow bone growth and development in upcoming visits. Child was normal in growth and development parameters at 6 month of follow up with the persistence of facial dysmorphism.

Discussion

Association of congenital anomalies with maternal warfarin use is well known. This condition is also known as Fetal warfarin syndrome (FWS) or warfarin embryopathy. The facial dysmorphism included hypoplasia of nasal bridge, laryngomalacia, pectus carinatum, congenital heart defects (atrial septal defect and patent ductus arteriosus), ventriculomegaly, stippled epiphysis, telebrachydactyly, and growth retardation [8]. There have been only few cases of acenocoumarol induced coumarin embryopathy reported [11–16]. Although, acenocoumarol is a known culprit for coumarin embryopathy but comparison of severity and dose related fetopathic effects with warfarin cannot be commented upon as number of cases for comparison is low. Table 1 show that nasal hypoplasia was present in all cases, stippled epiphysis were seen in four cases. One case had additional features like IUGR and hydrocephalus (Table 1). In our case, low birth weight, nasal hypoplasia, stippled epiphyses, distal phalangeal hypoplasia (2nd, 3rd,

4th) strongly support diagnosis of coumarin embryopathy. The baby had one episode of hypoglycaemia which has occurred due to poor feeding. There is known association between abnormal dermatoglyphics and distal phalangeal hypoplasia [17]. We did not find abnormal dermatoglyphics in present case, associated with distal phalangeal hypoplasia. Apart from these, the baby also had cephalhematoma despite being delivered without any perinatal complications and receiving vitamin K at birth. This could be accounted to the anticoagulant property of acenocoumarol. However, no other bleeding manifestations were noticed. None of the cases above mention the dose of acenocoumarol used during pregnancy, so it is uncertain whether the congenital anomalies have any dose dependent occurrence or not, as in case with warfarin [18].

In seven out of eight cases, exposure to drug was present in first trimester, making this period crucial for fetopathic on facial features and bone development. In one case, nasal hypoplasia was present even when the mother was not exposed to acenocoumarol in teratogenic window period [19]. This emphasizes the effect of coumarin derivatives can have on mid-facial development apart from gestational period of 8–12 weeks. This also challenges the currents regimen of substituting LMWH during first trimester as late exposure can also cause abnormal facial features.

Studies have been done on long term sequalae of coumarin exposure (acenocoumarol) on two cases where they found hypotelorism and disproportionate growth pattern in one baby who presented with stippled femoral epiphysis and nasal hypoplasia. Another baby had normal growth pattern but at 13 years of age had peculiar facial features due to persistence of midfacial hypoplasia. In both the cases neurological development was normal [3].

With this case report, we emphasize that acenocoumarol exposure during in utero period can cause bleeding complications like cephalhematoma apart from causing classical manifestations like midfacial hypoplasia, epiphyseal stippling and distal phalangeal hypoplasia. Association of acenocoumarol dose with occurrence of congenital abnormalities is unexplored. Comparison between fetopathic effects of warfarin and acenocoumarol is inconclusive as number of cases reported in acenocoumarol group is few. We need to generate registry and data to record fetopathic effects for such drugs so that valid comparison can be made to reach the conclusive remark. Use of LMWH during initial period of pregnancy does not guarantee against the impediment of occurrence of congenital abnormalities.

Authors' Contribution AS and AP collected the data and AS conceptualized the idea and wrote the manuscript and is first author. RP helped in case management and manuscript writing. OPM critically analysed the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declared that they have no conflict of interest.

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