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BRIEF COMMUNICATION

Fraser Syndrome: Prenatal Detection at 16 Weeks of Gestation

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Abstract Fraser syndrome is a rare autosomal recessive disorder characterized by syndactyly, renal abnormalities, genital malformation, and in some cases, cryptophthalmos. This syndrome had been diagnosed in the second pregnancy of a 22-year-old woman at 22 weeks of gestation based on prenatal scan, postnatal clinical examination, and autopsy findings. The third pregnancy was uneventful. In the fourth pregnancy, features of Fraser syndrome were evident in the first trimester 11–14 week aneuploidy scan. A review scan at 16 weeks of gestation confirmed the findings of Fraser syndrome. Early ultrasound diagnosis of recurrence of this syndrome as early as 16 weeks of gestation is highlighted.

Keywords Fraser syndrome · Cryptophthalmos syndrome · CHAOS · Renal agenesis · Consanguinity

Abbreviations

CHAOS	Congenital high airway obstruction syndrome
FRAS1	Fraser extracellular matrix complex subunit 1
FREM2	FRAS1 related extracellular matrix protein 2
GRIP1	Glutamate receptor interacting protein 1
NT	Nuchal translucency

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Introduction

Fraser syndrome is an autosomal recessive congenital disorder [1], which is very rare, having an incidence of 0.04 in 10,000 live-born infants and 1 in 10,000 stillbirths [2]. This condition is characterized by cryptophthalmos, syndactyly, laryngeal and genitourinary malformations, craniofacial dysmorphism, orofacial clefting, musculoskeletal anomalies and mental retardation. George Fraser in 1962 grouped the features and coined the term "cryptophthalmos syndrome". Cryptophthalmos is not always a feature of this syndrome and thus the eponym Fraser syndrome is preferable for this condition. It is also called Meyer–Schwickerath syndrome or Fraser–Francois syndrome, or Ullrich–Feichtiger syndrome. The primary etiology of Fraser syndrome is the mutation of FRAS1 gene [3] and it is occasionally caused due to FREM2 [4] and GRIP1 [5] gene mutations.

Report of Case

The first pregnancy of a 22-year-old woman with consanguineous marriage was terminated at 24 weeks and the review of ultrasound reports of the first pregnancy revealed suspicion of bladder outlet obstruction and ascites. During the second pregnancy, 22 weeks ultrasound study revealed bilateral hyperechoic enlarged lungs (Fig. 1a, b). The fetal heart was seen in midline, appeared compressed, and there was presence of ascites (Fig. 1c) suggestive of congenital high airway obstruction. Diaphragmatic inversion and flattening were seen. Single umbilical artery (Fig. 1d), unilateral renal agenesis, and reduced liquor were also noted. After counseling, the parents opted for termination of pregnancy. Postnatal evaluation revealed partial syndactyly of fingers (Fig. 2a), complete syndactyly of toes (Fig. 2b), and abnormal genitalia with

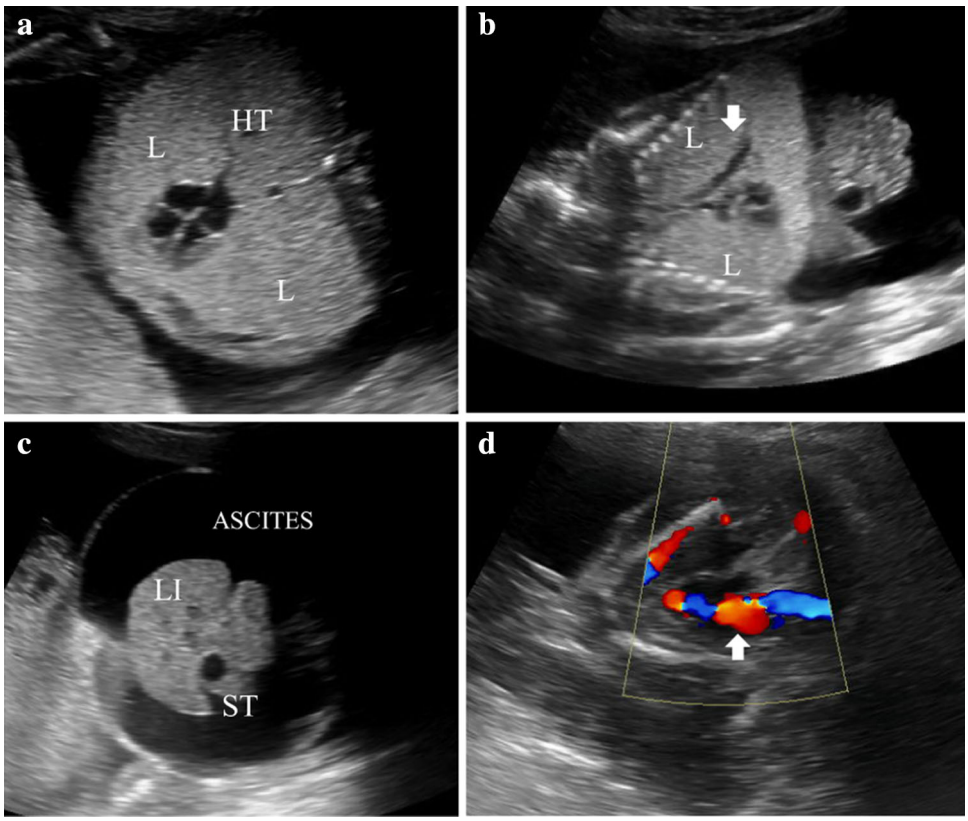

Fig. 1 Ultrasound images of 22 week fetus in second pregnancy. **a**, **b** Bilateral enlarged echogenic lungs (*arrow points* to dilated bronchus). **c** Ascites. **d** Single umbilical artery (*arrow points* to single umbilical artery)

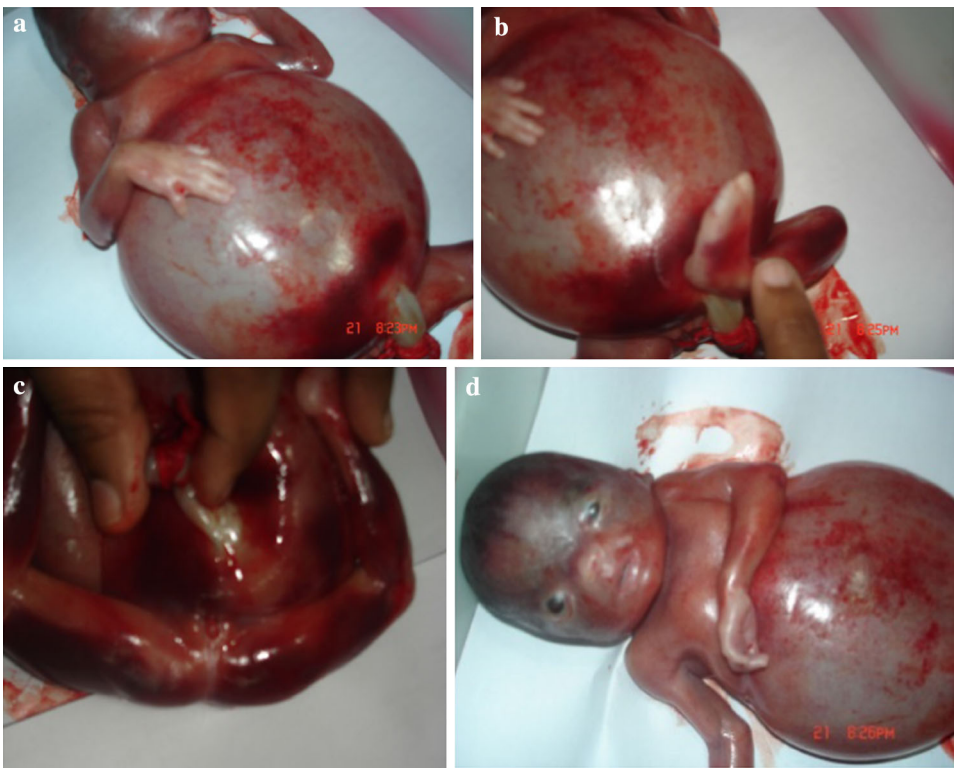

Fig. 2 Postnatal images of fetus with Fraser syndrome. **a** Partial syndactyly of 3rd and 4th fingers. **b** Complete syndactyly of toes. **c** Abnormal genitalia with imperforate anus. **d** Abortus showing wide open eyes with dysmorphic facies

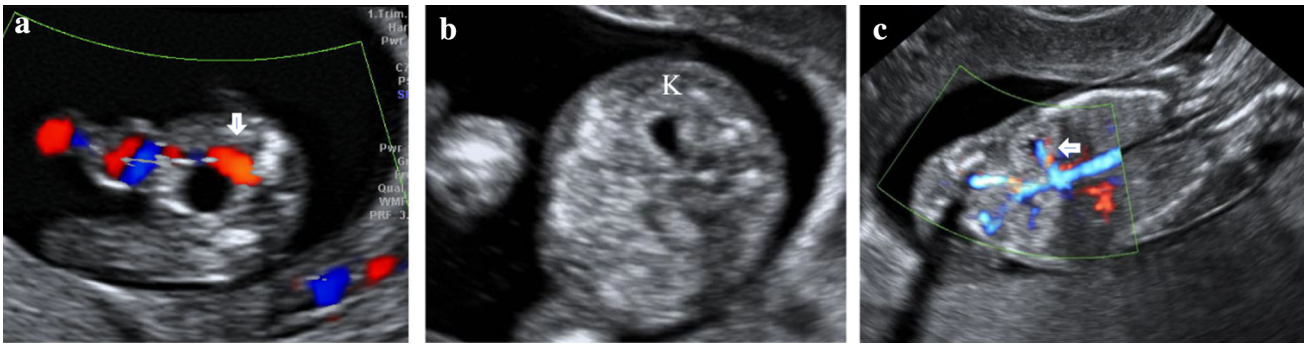

Fig. 3 Ultrasound images at 13 weeks in fourth pregnancy. **a** Single umbilical artery (*arrow points* to single umbilical artery). **b** Transverse section of kidney. **c** Unilateral renal agenesis (*arrow points* to unilateral renal artery)

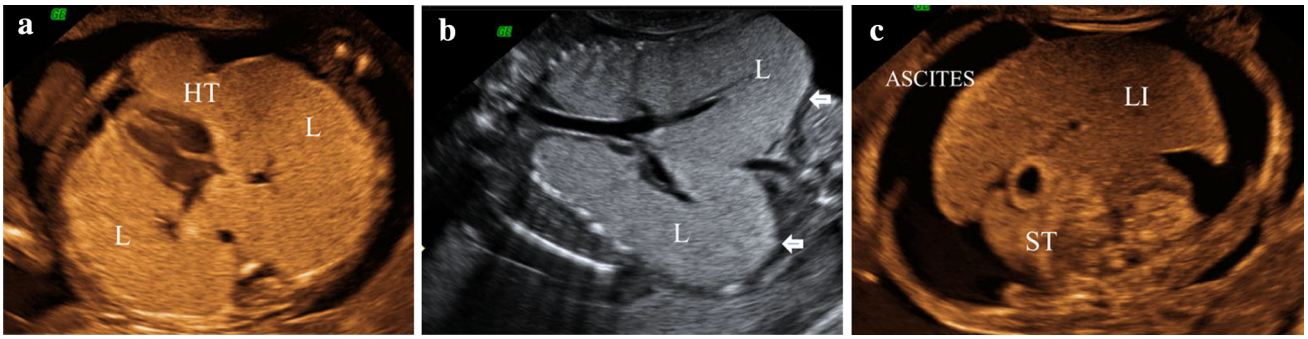

Fig. 4 Ultrasound images at 16 weeks in fourth pregnancy. **a** Bilateral echogenic lungs. **b** Dilated trachea and bronchi (*arrows point* to inversion of diaphragm). **c** Ascites. *Li* liver, *L* lung, *ST* stomach, *HT* heart, *K* kidney

imperforate anus (Fig. 2c). The face was severely dysmorphic with marked hypertelorism, depressed nasal bridge, and low set ears (Fig. 2d). A provisional diagnosis of Fraser syndrome was made based on the findings of syndactyly, abnormal genitalia, airway tract abnormality, and renal malformation. Later, autopsy confirmed the same.

The third pregnancy was uneventful. In her fourth pregnancy, the first trimester screening at 13 weeks revealed normal NT and single umbilical artery was noted (Fig. 3a). Evaluation of kidneys revealed suspicion of unilateral renal agenesis at 13 weeks as shown in Fig. 3b and c. In view of previous history, recurrence of Fraser syndrome was thought of and the patient was re-evaluated at 16 weeks of gestation. Ultrasound then revealed bilateral enlarged hyperechoic lungs (Fig. 4a) with ascites (Fig. 4c) suggestive of CHAOS, along with single umbilical artery and unilateral renal agenesis (Fig. 3c) proving recurrence of Fraser syndrome in her fourth pregnancy. Figure 3a–c illustrates ultrasound images at 13 weeks and Fig. 4a–c depicts images at 16 weeks of gestation. The patient was counseled and the possibility of recurrence of Fraser syndrome was explained. The couple opted for termination of pregnancy and autopsy confirmed Fraser syndrome.

Discussion

Frazer syndrome (OMIM No. 219000) has been described due to mutations in three genes—FRAS1, GRIP1, FREM2 [3]. The clinical spectrum of Fraser syndrome includes cryptophthalmos, cutaneous syndactyly, tracheal or laryngeal atresia, and genitourinary anomalies like renal agenesis, cryptorchidism, micropenis, clitoromegaly, craniofacial dysmorphism, orofacial clefting, mental retardation, and musculoskeletal anomalies [6].

Thomas et al. in 1986 were the first to propose the diagnostic criteria for Fraser syndrome, which include four major and eight minor criteria. The major criteria are cryptophthalmos, syndactyly, abnormal genitalia, and sibling with Fraser syndrome while the minor criteria are congenital malformation of ear, nose, and larynx, cleft lip with or without cleft palate, skeletal defects, umbilical hernia, renal agenesis, and mental retardation [7]. It helped to differentiate Fraser syndrome from isolated cryptophthalmos which is characterized only by the presence of fused upper and lower eyelids with micro-ophthalmos and also they stated that Fraser syndrome should be considered in the differential diagnosis of cases with multiple congenital

malformations, especially when they are associated with renal agenesis, even in the absence of cryptophthalmos [7]. Our case presented with multiple congenital malformations associated with renal agenesis without cryptophthalmos. Wide open right eye with hypoplastic lower eyelid was seen in the case and coloboma of upper eyelid was present in both eyes. Coloboma of the eyelid has also been reported as one of the ocular manifestation of Fraser syndrome.

van Haelst et al. [8] revised the diagnostic criteria stated by Thomas et al. [7] and suggested that diagnosis can be made, if either three major criteria or two major and two minor criteria or one major and three minor criteria are present in a patient. The major criteria were syndactyly, cryptophthalmos, urinary tract abnormalities, ambiguous genitalia, laryngeal and tracheal anomalies, and positive family history while the minor criteria were anorectal defects, dysplastic ears, skull ossification defects, umbilical abnormalities, and nasal anomalies. Cleft lip with or without cleft palate, cardiac malformations, musculoskeletal anomalies, and mental retardation were considered uncommon [8]. The present case fulfilled three major criteria stated by van Haelst et al. [8] by comprising renal anomaly, airway tract anomaly, and a previous history of Fraser syndrome. Fryns et al. [9] reported two male siblings with Fraser syndrome in second trimester at 23.5 and 18.5 weeks of gestation, respectively. Schauer et al. [10] documented the prenatal diagnosis of Fraser syndrome at 18.5 weeks of gestation, whereas from the present case report, it is evident that the prenatal diagnosis of CHAOS by ultrasound can be made in early second trimester at 16 weeks. If congenital high airway obstruction is unrecognized during the prenatal period, it usually results in stillbirth or death, shortly after delivery. Bilaterally enlarged hyperechoic lungs (Fig. 4a), dilated airways, and flattened or inverted diaphragm (Fig. 4b) are the typical prenatal sonographic findings. Fetal ascites and nonimmune hydrops can also be associated with the clinical condition.

Conclusion

Fraser syndrome is genetically heterogeneous due to mutations in three genes. However, a phenotype–genotype correlation has not yet been established for this condition and is clearly complicated by the rarity of the syndrome [11]. As Fraser syndrome is autosomal recessive in inheritance, there is a 25 % risk of recurrence in the future siblings. Hence, it is necessary to evaluate for features of Fraser syndrome early in the subsequent pregnancy. Ultrasound being a commonly used modality and its easy availability can be used to diagnose and to evaluate for recurrence of this syndrome. NT scan window can be utilized for early detection of anomalies and a meticulous search should be done at 13–14 weeks for evidence of recurrence in syndromes which have autosomal recessive inheritance. Alternatively, prenatal diagnosis can be carried out by molecular studies.

Compliance with Ethical Standards

Conflict of interest None.

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