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DOI: 10.1002/pd.767

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Prospective prenatal diagnosis of Fraser syndrome variant in a family with negative history

Fraser syndrome or cryptophthalmos-syndactyly syndrome is a rare autosomal recessive disorder including facial anomalies (cryptophthalmos, clefting, nose and ear abnormalities) laryngeal atresia, syndactyly, abnormal genitalia, renal agenesis and skeletal defects (Thomas *et al*., 1986). Additional reported anomalies include cerebral malformations, heart defects, major vascular anomalies, imperforate anus, intestinal hypoplasia and thymic aplasia (Ramsing *et al*., 1990). The prenatal diagnosis of Fraser syndrome is feasible and has been reported especially in case of positive family history (Thomas *et al*., 1986; Stevens *et al*., 1994; Berg *et al*., 2001); in families without positive history, the final diagnosis was reached prenatally only in four cases (Boyd *et al*., 1988; Serville *et al*., 1989; Stevens *et al*., 1994). We diagnosed Fraser syndrome in a fetus having, in addition to the anomalies commonly associated with the syndrome, a number of anomalies not described in any of the previously cited reports. For the type and the number of such uncommon anomalies, we hypothesize that it may represent a variant of Fraser syndrome.

A 31-year-old caucasian G0P0 woman, T.V., was referred to our Unit at 21 weeks' gestation of her first pregnancy because of an abnormal second-trimester routine scan. The family history of the parents was unremarkable. The ultrasound examination showed a fetus with multiple malformations and severe oligohydramnios. Laryngeal atresia with enlarged hyperechogenic lungs was diagnosed (Figure 1). In addition, we detected a conspicuous dilatation of the whole bronchial tree, with the trachea and the bronchi clearly visible, as in a bronchogram (Figure 1). Therefore, we hypothesized the presence of a tracheoesophageal fistula that allowed the fluid to migrate from the intestinal tract into the bronchial tree, where the laryngeal atresia blocked the upper airway, trapping the fluid within the bronchi. Additional anomalies included bilateral renal agenesis, pulmonary atresia with an intact ventricular septum, moderately severe rhizomesomelic shortening and hypotelorism with bilateral microphthalmia. The jejunum and ileum showed a proximal dilatation and intestinal hyperechogenicity, possibly indicating multiple atresias of vascular origin. There was no ascites. An accurate evaluation of the extremities could not be performed because of the severe oligohydramnios, but major bone abnormalities were absent, though it was not possible to exclude syndactyly. The putative diagnosis of a variant of Fraser syndrome was made. A diagnostic amnioinfusion and a cordocentesis for karyotyping were proposed but declined by the patient. After prenatal counseling, the couple opted for termination of pregnancy, performed at another institution located in the hometown of the couple. An X ray of the fetus was not performed. The pathology report described a highly macerated female fetus, in which the prenatally suspected anomalies were confirmed together with a unilateral cleft lip and palate, syndactyly of the left hand and bilateral clubfeet. On the basis of these findings, the diagnosis of Fraser syndrome was confirmed. The presence of tracheoesophageal fistula, duodenal and multiple ileal atresias as additional anomalies was also ascertained.

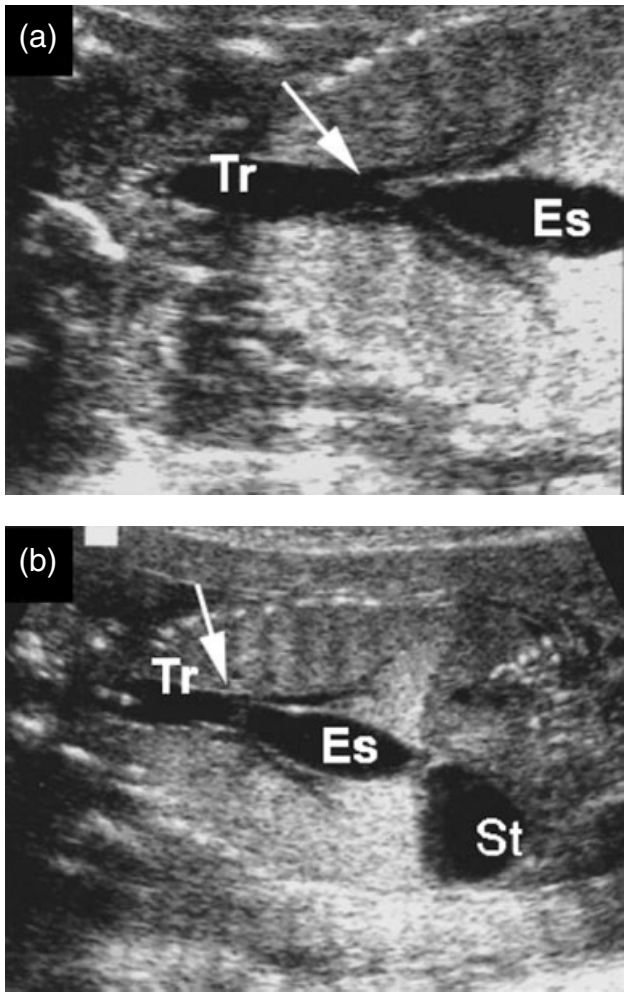

Figure 1—Coronal scan of fetal thorax and abdomen. (a) The dilatation of the bronchial tree (bronchogram) is evident. The arrow indicates the carina. (b) The image shows the communication between the esophagus and the trachea (arrow). (Es: esophagus; Tr: trachea)

Fraser syndrome has been known for more than a century. In 1986, Thomas (Thomas *et al*., 1986) established strict diagnostic criteria (major and minor) for the diagnosis of Fraser syndrome after birth. However, these criteria can not apply to the cases diagnosed prenatally; in fact, *in utero*, all major criteria (cryptophthalmos, syndactyly, abnormal genitalia; nasal and ear anomalies) are demonstrable with difficulty in the presence of severe olygohydramnios, owing to the common presence of bilateral renal agenesis. Therefore, prenatal diagnosis of the syndrome relies almost entirely on the detection of some of the minor criteria (congenital malformations of the nose, ears, larynx, cleft lip and/or palate, skeletal defects, umbilical hernia, renal agenesis).

As to the differential diagnosis, the association of laryngeal atresia with renal agenesis and/or microphthalmos is so unusual that it leads to the final diagnosis. Laryngeal atresia is characterized by the presence of brightly echogenic and severely enlarged lungs with or without ascites. The differential diagnosis with congenital cystic adenomatoid malformation type III, diaphragmatic hernia, and intralobar sequestration is straightforward, for these malformations are almost always unilateral, while laryngeal atresia affects, by definition, both lungs. Renal agenesis, which is present in 85% of cases, is diagnosed for the association of severe olygohydramnios with empty renal fossae. The only anomaly for which the differential diagnosis may be difficult is microphthalmos, since this anomaly is a feature of numerous syndromic conditions, the most common being trisomy 13. In fact, microanophthalmia characterizes COFS (Cerebro-Oculo-Facio-Skeletal) syndrome, Walker–Warburg syndrome and Hallermann–Streiff syndrome. However, the occurrence of laryngeal atresia or renal agenesis has never been described in any of these disorders.

The last issue to discuss regards the occurrence, in the present case, of the gut anomalies. The only gastrointestinal malformation that has been described in Fraser syndrome is anal atresia (Ramsing *et al*., 1990). Since the intestinal abnormalities detected in the index case, namely, tracheoesophageal fistula, duodenal atresia and multiple jejunal atresias, have never been reported in Fraser syndrome, we believe that the case described here might represent a variant of the syndrome.

Taking into consideration the clinical heterogeneity of this pathologic entity (Rousseau *et al*., 2002), the awareness of the various malformations that may characterize Fraser syndrome in the fetus is of utmost importance for a correct prospective prenatal diagnosis especially in families with negative history. In fact, of all the reports regarding the diagnosis of Fraser syndrome in families with negative history, the final diagnosis was reached prenatally only in four instances (Boyd *et al*., 1988; Serville *et al*., 1989; Stevens *et al*., 1994); the present case being the fifth. In the other reports, only the association of the various anomalies was described prenatally, with the final diagnosis of Fraser syndrome being reached only at necropsy.

In conclusion, we have described a case of prospective prenatal ultrasound diagnosis of Fraser syndrome in a family with negative history. We believed that it was worth reporting because it may represent a variant of the syndrome, for the associated gastrointestinal anomalies have never been reported in Fraser syndrome and because the final diagnosis was prospectively reached *in utero* on the basis of the ultrasound findings.

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DOI: 10.1002/pd.769

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Coping with termination of pregnancy for fetal abnormality

The outcome of the further development of prenatal diagnostics is that fetal abnormalities are being increasingly diagnosed and the prognosis assessed in the first and second trimesters of pregnancy. However, many disorders still have only restricted access to prenatal therapy. Although the number of women having to make a decision on induced abortion is increasing as a result of improved prenatal diagnostics, the psychological responses of women following the diagnosis of fetal anomaly and subsequent induced abortion remain relatively unexplored.

Against this background, the study by Geerinck-Vercammen and Kanhai (2003) on coping with termination of pregnancy (TOP) for fetal abnormality in a supportive environment provides valuable information, especially as the authors included not only the women