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ORIGINAL ARTICLE

Indications of 1342 Fetal Cord Blood Sampling Procedures Performed as an Integral Part of High Risk Pregnancy Care

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Abstract

Background Fetal umbilical cord blood sampling is now being performed worldwide, using an ultrasound guided technique, for prenatal diagnosis in pregnancies at high risk for several congenital and genetic defects in the fetus. Awareness of feasibility of the procedure and indications for the same should be known to every obstetrician.

Aims and Objectives To study the indications for Fetal Cord Blood Sampling in high risk pregnancy patients in the last 20 years at a tertiary referral center in India.

Materials and Methods Women referred to the Fetal Medicine Clinic for fetal blood sampling from January 1990 to November 2009, were assessed. An informed consent was taken. Under continuous ultrasound guidance, a 22 gauge long spinal needle was inserted through the maternal abdomen and uterine wall into the umbilical cord, and about 2–4 ml of blood, depending on the indication was aspirated by syringe. The various indications for fetal blood sampling in 1342 women were analyzed.

Results Cord blood sampling was performed for the following indications: Hb in Rh Isoimmunized pregnancies—553 cases, Chromosomal analysis—427 cases, non-immune hydrops/pleural effusion/ascites—cases 88, Congenital Infections—131 cases, Intrauterine Growth Restriction—51 cases, Thalassemia—53 cases, Hemophilia—36 cases, and for Thyroid function test for fetal goiter in 3 cases, in total 1,342 women.

Conclusion There were several absolute indications for fetal cord blood sampling in high risk pregnant women, to provide state-of-the-art information on the health of the fetus. Awareness of the procedure and indications for the same should be known to every obstetrician as it is technically feasible, expertise is available in India; so that women who require the procedure may be referred in time.

Keywords Cord blood sampling · Indication · Ultrasound

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Introduction

High risk pregnancies (HRP) include maternal factors like diabetes, hypertension, previous poor outcome; and those pregnancies where the fetus is at risk of a congenital malformation, chromosomal anomaly or genetic disease. Prenatal diagnosis of 2–5 % of all pregnancies with several congenital and genetic defects is now an important component of Antenatal Care. Care of HRP includes ultrasound and biochemical screening for congenital defects. There is suspicion that the fetus is at high risk of having a chromosomal anomaly in the presence of ultrasound structural malformations (duodenal atresia, non-immune hydrops,

and congenital heart disease), severe anemia (Rh-isoimmunised mother and ultrasound features like hydrops, raised middle cerebral artery Doppler,) positive biochemical screen for Down Syndrome, fetal infection, etc. Confirmation of fetal disease is by tissue diagnosis from amniotic fluid, chorionic villi or cord blood.

Fetal tissue sampling was a possibility with amniotic fluid and chorion villus sampling. However, obtaining fetal blood samples for conditions not easily diagnosed by these two procedures remained a challenge. Obtaining pure fetal blood by fetoscopy in the second trimester of pregnancy was a reality by 1978, when Rodeck and Campbell described a technique for fetal blood-sampling between 16 and 22 weeks' gestation combining fetoscopy with real-time ultrasound in 48 attempts at fetal blood-sampling [1]. The fetal loss rate was 3.7 %, judged to be due to fetoscopy [2, 3]. The breakthrough came in the form of the "percutaneous ultrasound-guided fetal blood sampling (PUFBS)", "cord-blood sampling" or cordocentesis. Fetal blood sampling via the umbilical cord using a needle guided by ultrasound was first reported by Daffos et al. [4], and subsequently by Nicolaides and Rodeck [5]. In India, fetal blood sampling and in utero transfusion was first performed by Buckshee et al. [6].

State of the art cord blood sampling is now routinely performed for various reasons, and the patient load is increasing everyday [7–10]. It is important to realize the possibility of antenatal diagnosis of various fetal conditions from fetal cord blood, and understand the indications for which the procedure should be recommended. We present and discuss the indications for 1342 Fetal Blood Sampling procedures performed as an integral part of High risk pregnancy Antenatal Care in the last 20 years, at a tertiary referral center in India.

Materials and Methods

Women who were referred to the Fetal Medicine Clinic for fetal blood sampling from the High Risk Pregnancy, Genetic and Hematology and other Clinics, and from several parts of India, were re-assessed for the need of cord blood sampling. An informed consent was taken, briefly describing the indication and need for the procedure, and the risk of fetal loss as generally 1 %, but that it could be more depending on the background fetal condition—such as in hydrops fetalis and severe congenital malformations.

A detailed ultrasound scan using 3.5 MHz 2D color Doppler probe was first performed for the fetal heart activity, period of gestation, number of fetuses, liquor volume and fetal anomalies. Special attention was paid to the location of the placenta and the cord insertion site. The needle path towards the most accessible and convenient part of the cord, preferably the placental insertion site, into which the needle could be inserted was searched for and mapped.

Cordocentesis was done as an outpatient facility unless a procedure like fetal blood transfusion was to be carried out. The patient was kept in the supine position. Under all aseptic and antiseptic care, the abdomen was cleaned and draped. The transducer was prepared in a sterile fashion. The cord was again identified at the targeted site with Color Doppler and local anaesthetic infiltrated over the skin at the marked needle insertion site.

Under continuous ultrasound guidance, a 22 gauge long spinal needle was inserted through the maternal abdomen and uterine wall. With a sharp thrust the needle tip was inserted into the umbilical vein in the cord at about 1–1.5 cm from its insertion into the placenta, or at the most easily accessible site in free loop (Fig. 1). When the needle tip was visualized inside the vein, the stellate was withdrawn, a 2–5 cc syringe was attached to the hub of the needle carefully, and the required volume, about 2–4 ml of blood depending on the necessity of indication was aspirated. The sample was injected into a vacutainer or bottle filled with the appropriate anticoagulant.

The fetal heart was observed for any tachycardia or bradycardia—its duration and intensity. The duration of funicular bleeding was also noted. Sometimes, if fetal movements were anticipated to interrupt or be bothersome during the sampling procedure as in a posterior placenta, or when a free loop of cord was to be sampled, vacuronium or pancuronium (0.3 mg/kg estimated fetal weight) was injected into the fetal thigh or buttock with a 23 gauge needle or into the cord. This paralysed the fetus for 30–60 min, enabling the procedure to be performed smoothly without risk of needle dislodgement or rent in the cord because of fetal movement.

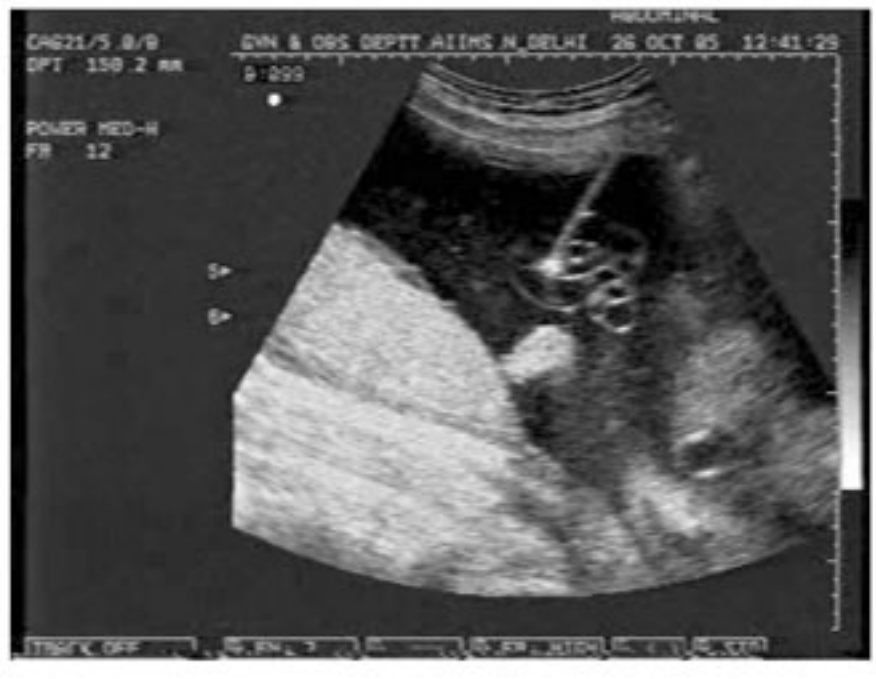

Fig. 1 Cordocentesis showing needle in free loop of umbilical cord, posterior placenta

Results

Cord blood sampling was performed in 1,342 women from January 1990 to November 2009, in one unit dealing with Fetal Medicine. The various indications of cordocentesis are shown in Table 1.

Discussion

Prenatal diagnosis by percutaneous umbilical blood sampling (PUBS) has rapidly gained popularity as it provides a new minimally invasive and exciting method for assessment and management of certain fetal disorders [7, 11, 12], but is still being performed in very few Centers in India. This procedure offers direct access to the fetal circulation for obtaining blood samples or for transfusing the fetus in utero, and promises treatment approaches that were not previously available, so as to prolong pregnancy, resulting in decreased prematurity and mortality rates as for infants with erythroblastosis fetalis [7]. If the suspected diagnosis could also be made by amniotic fluid or chorion villus sampling as for intrauterine infections or karyotype, the latter were advised depending on the case, and the period of gestation at presentation.

Rh isoimmunization was the most common indication for cord blood sampling at our center—for hemoglobin, hematocrit, blood group. Cordocentsis is performed when Middle Cerebral Artery peak systolic velocity MoM is >1.5, there is an ultrasound evidence of fetal anemia or fetal hydrops (Fig. 2). Fetal blood transfusion is carried out if the hematocrit is <30 % [13].

In India, B Thalassemia (not A Thalassemia) and hemophilia are common genetic disorders for which prenatal diagnosis is now available. PND is increasingly being done by DNA analysis of chorionic tissue. The diagnosis had earlier been done by the procedure of cord blood sampling and globin chain analysis, but is now restricted to cases when mutations have not been identified, use of HbA estimation by CE-HPLC for prenatal diagnosis of beta-thalassemia [14–17].

Spontaneously dividing nucleated erythrocytes present in prenatal cord blood samples can be used for rapid chromosomal analysis, to give karyotype within 24 h for indications like advanced maternal age, positive biochemical screen, previous child with Down Syndrome, parental balanced translocations, etc. Cordocentesis are now performed mainly in advanced gestations or when there is confusion over the chorionic villi or amniocentesis results. For assessment of mosaicism found on amniotic fluid or chorionic villi cultivation, if normal karyotype is diagnosed on fetal blood, continuation of pregnancy is safe and to be recommended.

Percutaneous ultrasound-guided fetal blood sampling was reported to be performed on 100 pregnancies with various fetal problems; in 43 cases, a positive diagnosis was established for 25 Hemoglobin Bart's hydrops fetalis, 2 beta-thalassemia major, 1 hemophilia, 1 rubella infection, 1 syphilis and 13 chromosome aberrations [11]. Pure fetal blood was obtained in another series of 101 fetuses of 96 patients at 15–38 weeks' gestation [12]. Rapid karyotype was obtained within 2–4 days by fetal lymphocyte culture. Chromosomal abnormality was detected in 12 (11.9 %) foetuses—in five of 44 fetuses with structural malformations, three of 13 fetuses with intrauterine growth

Table 1 Indications for cord blood sampling (Jan. 1990–Nov. 2009)

	Indication	No. of procedures
1.	Rh-isoimmunization	553
2.	Karyotype:	*427*
	Structural malformation	297
	Previous child chromosomal abnormality	88
	Increased maternal age	10
	Abnormal biochemical screen	17
	Balanced translocation in parents	2
	Inconclusive CVS/Amnio for karyotype	13
3.	Non-immune hydrops	76
	Pleural effusion	4
	Ascites	8
		88
4.	Congenital infections (TORCH)	131
5.	IUGR	51
6.	Thallassemia	53
7.	Hemophilia	36
8.	Thyroid function test for fetal goiter	3
	Total	1,342

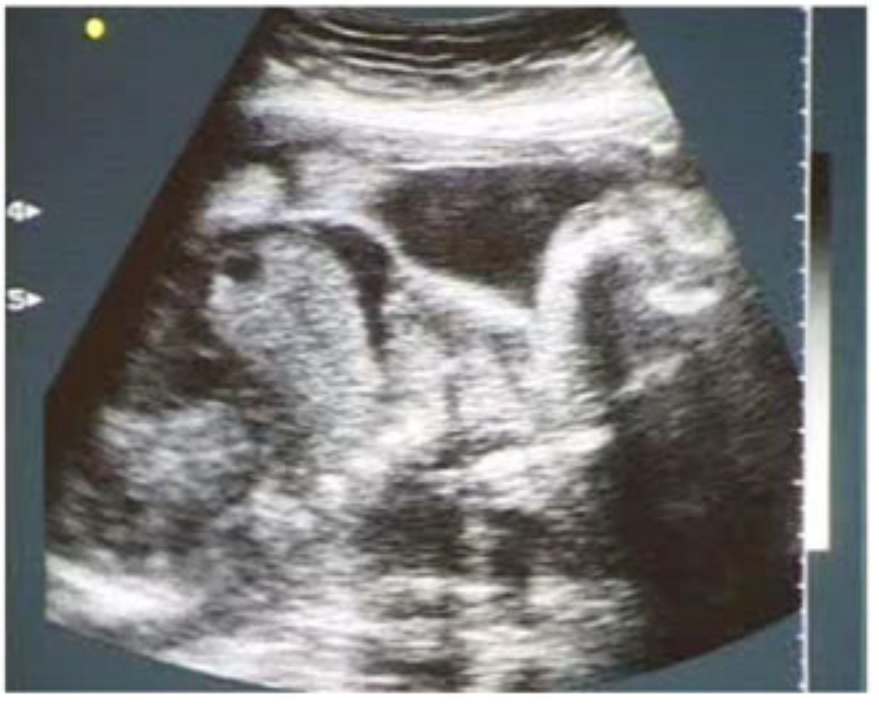

Fig. 2 Ultrasound showing fetal hydrops in Rh-immunisation

retardation or oligohydramnios, one of three fetuses with non-immune hydrops fetalis, two (one monozygotic set) of 10 discordant twins, one of 12 isoimmunized gestations, none of eight cases with advanced gestational-maternal age, and none of six immune thrombocytopenia cases.

When a fetal congenital abnormality is diagnosed on ultrasound, the knowledge of the fetal chromosomal constitution is important for the management, genetic counseling, cost benefit, and epidemiological aspects; especially when the malformation is associated with high risk of chromosomal anomaly such as in duodenal atresia, non-immune hydrops, heart disease, etc. The incidence of aneuploidy in fetuses with detectable ultrasound abnormalities ranges from 16.8 to 45 % [7, 8]. Cord blood sampling gives a better and quicker chromosomal preparation than with chorion villus biopsy or amniocentesis. The abnormal karyotypes usually obtained are trisomy 13, 18, 21; triploidy, 45 X, or other rarer patterns. In India, most cases are referred at later stages of gestation, when termination of the pregnancy is not possible due to ethical reasons. Obtaining a karyotype can at least prevent a cesarean section for fetal indication, or deter heroic attempts at fetal surgery. It will also help in genetic counseling for the future if postmortem cultures fail in the event of fetal demise [18].

Cord blood sampling is indicated when specific maternal TORCH IgM titers are positive or IgG titers rise significantly, there is a fetal structural anomaly such as hydrocephalus, symmetrical growth restriction or non-immune hydrops. Serology, direct identification of the viral particles by electron microscopy of fetal blood, cultures of fetal blood, and indirect parameters like platelet count, total leukocyte count, differential count, liver enzymes are carried out to arrive at a diagnosis [19].

As ultrasound is being done in most pregnancies, non-immune hydrops which is very easy to pick up on US (Fig. 3), is being diagnosed. Management of a case of NIH is a real obstetric challenge because the condition is a very nonspecific finding, and there are multitude of causes, and is associated with a very poor prognosis. Non-immune hydrops fetalis (NIH) appears to be very common in India, and requires extensive workup for the cause with ultrasound, fetal echocardiography; amniocentesis and cordocentesis. Cord blood sampling should be carried out for fetal karyotype, intrauterine infections, biochemical diseases—congenital disorder of glycosylation type Ia (CDG-Ia), fetal xerocytosis, lysosomal storage diseases [20]. Treatment of non-immune hydrops fetalis due to fetal parvovirus B19 infection by fetal blood transfusion, albumin transfusion in non-immune fetal hydrops may be performed through the cord [21].

Intrauterine Growth Restriction (IUGR) of the symmetrical or early onset type needs an evaluation to exclude

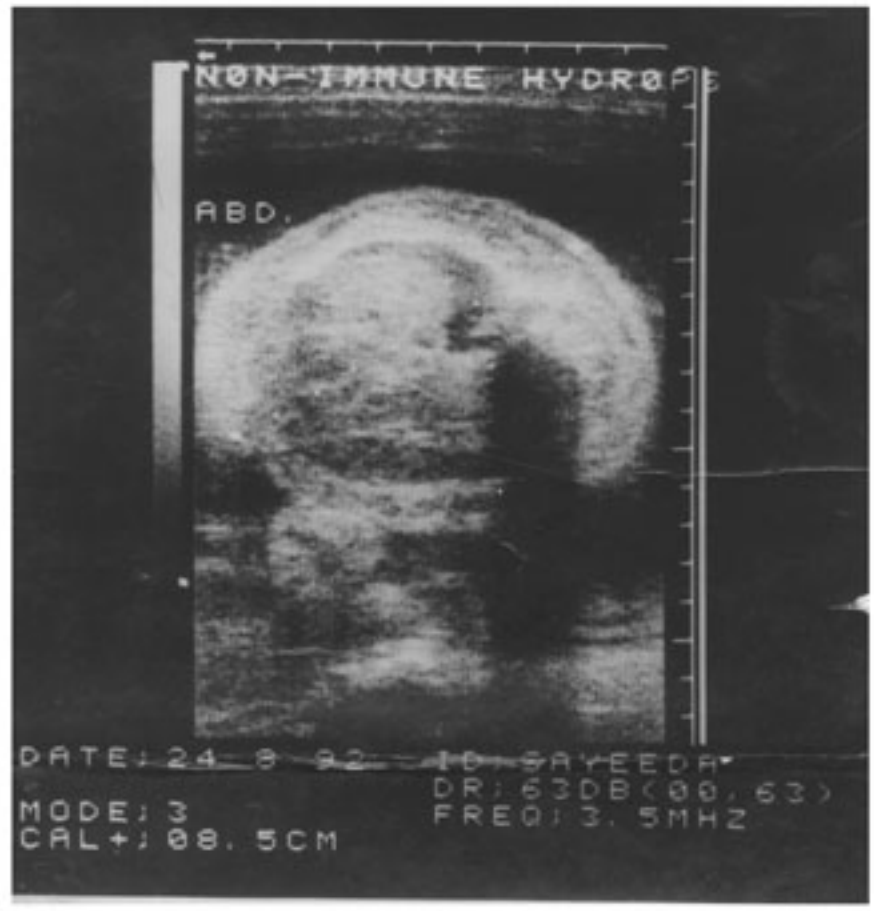

Fig. 3 Ultrasound of transverse view of fetal abdomen showing non-immune hydrops

a chromosomal anomaly, intrauterine infection, or early uteroplacental insufficiency. In a series of 71 singleton pregnancies with asymmetrical growth restriction diagnosed at 15–35 weeks gestation, the fetal karyotype was abnormal in 7 (9.9 %) of the cases [8]. The incidence of chromosomal abnormalities in asymmetrical IUGR fetuses with structural defects was 21 % (4/19). The incidence of fetal aneuploidy in structurally normal fetuses with asymmetrical growth retardation detected before 23 weeks gestation was 20 % (3/15); while for those presenting between 23 and 29 weeks gestation, no abnormal karyotypes were found suggesting that fetal karyotyping may be unnecessary in structurally normal fetuses with early onset IUGR occurring between 23 and 29 weeks of gestation. Now-a-days, cord blood sampling is not done for acid–base status, as the biophysical profile and Doppler Velocimetry are very reliable non-invasive indicators.

Cordocentesis is also a novel method of directly delivering appropriate medication to the diseased fetus. An intravascular fetal blood transfusion is very useful in a management of fetal anemia due to Rh immunization or hemorrhage, as is albumin infusion in hypoalbuminemic states of nonimmune hydrops [22].

In conclusion, there are a multitude of indications for fetal cord blood sampling, to provide state-of-the-art information on the condition of the fetus that cannot be obtained by other techniques of prenatal diagnosis. Cordocentesis has tremendous fetal diagnostic and therapeutic applications, and exciting research potential. It is technically

feasible, and has become an important, indispensable tool in the management of HRP worldwide and in India. Awareness of the procedure and indications for the same should be known to every Obstetrician, so that women who require the procedure may be referred in time.

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