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Prenatal Diagnosis in Service of Mankind

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Abstract: ***Prenatal Diagnosis means diagnosis before birth. The fundamental philosophy of prenatal diagnosis is to provide reassurance to couples at risk that they may selectively have unaffected children even if their perspective risk for having defective offspring might be unacceptably high. The incidence of birth defects or genetic disorders in pregnancy is approximately 3%. Some will be found to have congenital or genetic defect during childhood or early adulthood. Recent advances in technology have enabled the development of a wide range of methods for prenatal diagnosis. The desire of every couple is to have a 'perfect' healthy normal baby. Prenatal testing and its perceived benefits have been in focus for a long time. There has been widespread debate and passionate arguments on both sides. In India, where the law allows termination of pregnancy before 20 weeks, there are several prenatal tests that are available only after 20 weeks. This dichotomy produces considerable anxiety and stress to would be parents who may need such information within the legal timeline for pregnancy termination.***

Keywords: Prenatal Diagnosis, Birth defect, Congenital defect, Genetic defect

1. Introduction

The fundamental philosophy of prenatal diagnosis is to provide reassurance to couples at risk that they may selectively have unaffected children even if their perspective risk for having defective offspring might be unacceptably high[16]. The incidence of birth defects or genetic disorders in pregnancy is approximately 3% [24]. The understanding and selection of prenatal diagnostic technique requires an understanding of the causes of congenital anomalies and genetic defects. The selection of disorders to be detected is an essential step in the construction of an efficient diagnostic plan. The objectives of the prenatal diagnosis are:

1) To offer the widest possible range of choices to women at risk of having children with a genetic abnormality.
2) To provide reassurance and reduce the anxiety associated with reproduction, especially among high risk women.
3) To enable high risk women to continue a pregnancy by confirming the absence of a certain genetic disease.
4) To facilitate optimal treatment of affected infants through early diagnosis.

Screening and Indications for Prenatal Diagnosis

The first step in efficient prenatal diagnosis workup is preconceptual counselling, which may identify risk factors of maternal or paternal medical disorders, exposure to teratogens or adverse lifestyles and family history. Screening for genetic disorders can be performed when there is a positive family history. Certain racial and ethnic groups are at an increased risk for specific disorders such as hemoglobinopathies in India, and carrier screening should be considered. Detection of carriers or affected states is possible using a variety of biochemical testing and recombinant technology. In situations where one partner is a carrier of a dominant disorder, gamete donation or Preimplantation diagnosis are important considerations. Indications for prenatal diagnosis are:

1) Family history for a genetic disease. It is the single most important tool for assessing genetic risk for single genetic disorders.
2) Advanced Maternal age (>35 years of age)
3) Previous child with a chromosomal abnormality
4) Abnormal Ultrasound findings
5) Positive Maternal serum marker screen
6) Parental Chromosomal rearrangement
7) History of unexplained repeated foetal losses or unexplained perinatal death.

Prenatal Diagnostic / Screening Techniques

There are several prenatal diagnostic and screening techniques available. Prenatal diagnostic techniques are invasive whereas screening techniques are non-invasive. Invasive techniques carry a small but significant risk to the pregnancy. Prenatal diagnostic and screening techniques differ in their invasiveness, risks, accuracy, cost, optimal time of performance and appropriateness for a given condition.

1) **Ultrasonography**: It is a much utilised tool for the detection of fetal anomalies. New developments include high resolution units and transvaginal probes, which enable visualization of the foetus as early as 5 weeks gestation. It is used for a thorough system evaluation which can be performed early in gestation at around 15 weeks or later at 20-22 weeks. Diagnostic accuracy is operator dependant. Ultrasound is also used for guidance in invasive diagnostic procedures. Other imaging techniques include magnetic resonance imaging (MRI) which is used mainly for imaging of the central nervous system, in rare situations.
2) **Maternal Serum Screening**: It has been established as a valuable prenatal screening method. There is an association between a low maternal serum alpha feto-protein (MSAFP) and an increased risk of trisomy 21. Combining MSAFP and maternal age with the human chorionic gonadotropin (hCG) and with or without unconjugated estriol (E3) provides the most effective screening method available, identifying approximately 70% of Down's syndrome cases, with a false positive rate of 6.6% [11]. Triple marker screening is now routinely used in many countries. New refinements have enabled the diagnosis of trisomy 18 on the same blood sample [2]. An abnormal marker screening test is an indication for amniocentesis.
3) **Chorionic Villus Sampling (CVS)**: It has been in wide use since 1980s, to obtain material for cytogenetic analysis, through culture or FISH and for biochemical

studies[5]. CVS has a loss rate greater than one cited for amniocentesis, approximately 2.0%, but in well experienced hands the loss rate is expected to be smaller[19]. CVS can be performed transbdominally and transcervically under ultrasound guidance with equal safety, usually between 9 and 12 weeks gestation[13]. CVS is used for both chromosomal and DNA based diagnosis. It is preferred diagnostic mode for biochemical abnormalities, since a larger amount of fetal tissue can be obtained. Reported complications include vaginal bleeding or spotting, rare infections from accidental passage through the intestinal flora and rare rupture of membranes. Limb reduction defects [9][17] and placental mosaicism upto 3% [23] have also been reported.

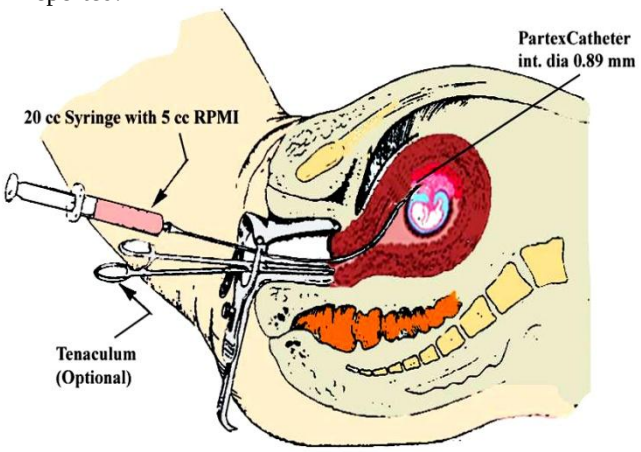

Figure 1: Chorionic Villus Sampling (Cervical)

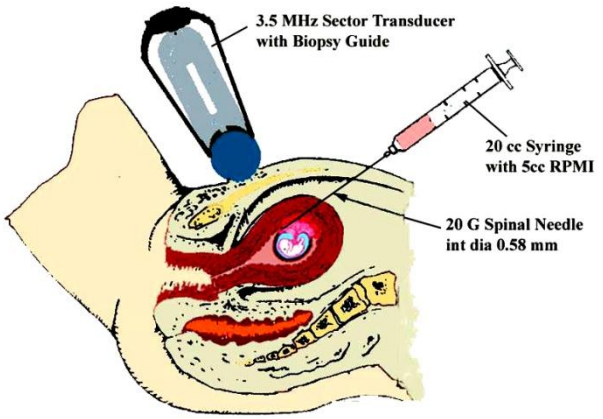

Figure 2: Chorionic Villus Sampling (Abdominal)

4) **Amniocentesis**: It has been performed as a prenatal diagnostic measure since 1950s and with aid of ultrasound guidance since the 1970s [4]. In western countries amniocentesis is offered to all women who will be 35 years of age or older at their expected time of delivery. Amniotic fluid cells are used for detection of chromosomal abnormalities and also for DNA based diagnosis for single gene disorders. Amniocentesis is also recently applied in cases of premature labor and premature rupture of membranes for diagnosis of subclinical intrauterine infection [22]. Amniotic fluid measurement of lecithin sphingomyelin ratio and phosphatidylglycerol level has been widely used for assessment of fetal lung maturity, but is now clearing the place for better methods of ultrasound assessment of gestational age and fetal surveillance [6]. Complications of amniocentesis can include amnionitis, amniotic fluid leakage, vaginal bleeding, cramping and lower abdominal discomfort, which may persist for upto 48 hours. A controlled randomized trial which assessed the safety and accuracy of amniocentesis reported a fetal loss rate of 1.7% in the amniocentesis group vs 0.7% in the control group although the rate is thought to be less. Culture failure occurs in less than 1% of cases and chromosomal mosaicism in 0.5% [4]. Early amniocentesis can be performed between 9-14 weeks gestation, compared to usual amniocentesis which is performed between 15-18 weeks gestation. It is safe alternative to CVS and is considered close in safety to regular amniocentesis. A potential advantage of early amniocentesis over CVS is the ability to perform biochemical testing for neural tube defects, but the utility of this is not yet clear [4]. The loss rate is about 2-3% [7] [18]. The culture failure rate is approximately 0.255 [4]. Other reported complications include bleeding, fluid leakage and cramping [12]. Attempts at very early amniocentesis are hampered by the limited quantity of amniotic fluid available for sampling and a proportional paucity of fetal cells. Only 5 ml of fluid can be recovered between 7-10 weeks, after which more than 10 ml are obtainable [14].

5) **Fetal Blood Sampling or Cordocentesis**: It is generally performed by percutaneous umbilical blood sampling under ultrasound guidance. Common indications include rapid karyotype determination, assessing the Rh isoimmunisation status, ruling out fetal infection, evaluation of fetal acid base status, platelet count or twin-to-twin transfusion syndrome. Karyotype is available from fetal white blood cells in 48-72 hours. The fetal loss rate varies widely depending on the operator and is generally cited to be around 2%. The main complications are chorioamnionitis, membrane rupture, bleeding from the puncture site, severe bradycardia and thrombosis [4]. Cordocentesis is generally not recommended for growth retarded foetuses as they tend more to develop fetal distress necessitating caesarean section [4]. Cordocentesis can also be used for fetal therapy in cases of anemia or thrombocytopenia. In future, antenatal stem cell transplantation may be used.

Fetoscopy and embryoscopy is used sporadically for diagnosis of specific disorders, for example dermatoses or hepatic dysfunction [3][10]. The method involves introduction of small fibre optic equipment for visualization [20] and is still considered experimental.

Fetal biopsy has largely cleared its place in favour of enzyme assay or DNA analysis in amniotic fluid cells or chorionic villi [4]. However, when DNA analysis is not informative, biopsy may be the only diagnostic option. It is expected that in future when more disorders will become detectable by DNA analysis, less biopsies will have to be performed. Possible current options include fetal skin sampling for the diagnosis of genodermatoses, fetal liver biopsy and fetal muscle biopsy in case of Duchenne muscular dystrophy (DMD) [8]. The procedure is performed between 17-20 weeks gestation under continuous ultrasound guidance. Possible complications include spontaneous

abortion, amniotic fluid leakage, hemorrahage, infection, prematurity and fetal cosmetic injury [4]. Fetal loss in experienced hands is approximately 5% [21].

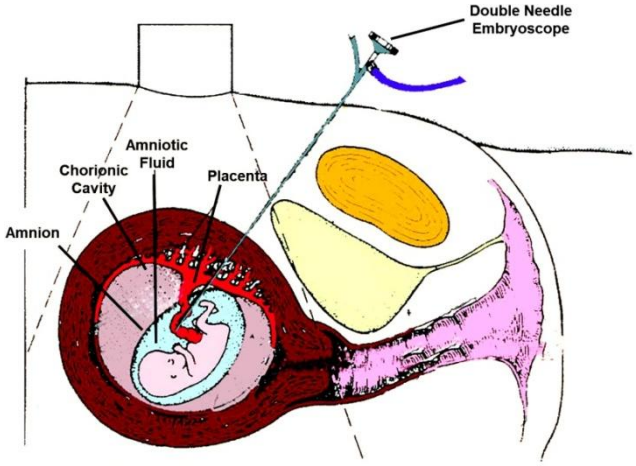

Figure 3: Double barrel needle embryoscope inserted transabdominally into the amniotic cavity to perform fetal blood sampling / tissue sampling

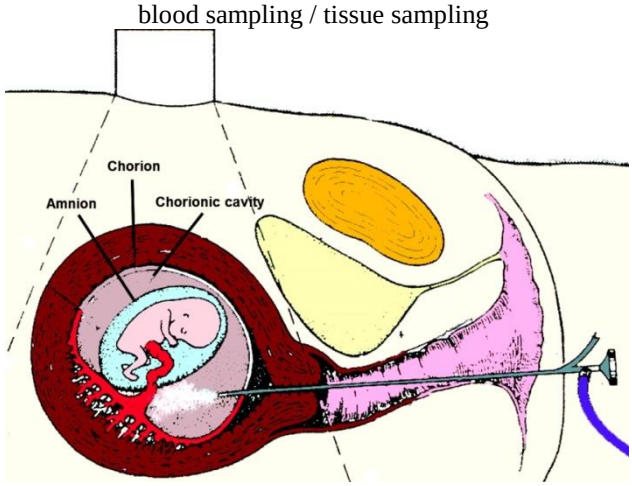

Figure 4: Transcervical Embryoscopy Technique

Recent Technique-A step ahead of Prenatal Diagnosis

1) **Preimplantation Diagnosis:** Itis a relatively new option for prevention of genetic disease states, aimed at selecting healthy zygotes while rejecting affected ones. Available techniques include polar body, blastomere or blastomere biopsy. Preimplantation diagnosis is high costs and generally performed through assisted reproduction which is not used by all couples. Furthermore, Preimplantation diagnosis is generally performed through assisted reproduction which is not used by all couples.
2) **Fetal Cells in Maternal Blood samples:** It can be obtained for analysis. Approximately one fetal cell exists per million total maternal cells in 1 ml of blood, but variation is wide [25]. Different types of fetal cells can be found in maternal circulation, such as trophoblasts, erythroblasts and lymphocytes. The target of studies in this field is accurate sexing of the fetus, obtaining material for molecular studies by PCR and obtaining cells for fluorescent in situ hybridisation (FISH). A disadvantage of this technique is that cells from a previous pregnancy or spontaneous abortion may remain in the circulation and cloud the analysis. Successful detection of trisomy 21 has been shown by this method [1].

2. Conclusion

In conclusion, it can be said that prenatal testing can be a boon not only to alleviate anxiety, but also in helping parents make a choice about the foetus in a manner that would be more mentally, emotionally and rationally acceptable.

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