INTRODUCTION

Congenital heart diseases (CHDs) are the most common fetal congenital malformations, having a rate 6 times greater than chromosomal aberrations and 4 times greater than neural tube defects ***(Carvalho et al., 2002).***

Third of these anomalies are found at birth, the incidence of congenital heart disease is estimated to be 8-12 in 1000 live births ***(Barboza et al., 2002).***

20% of neonatal deaths and 50% of infant deaths due to malformations are due to cardiac anomalies, Therefore diagnosis of cardiac diseases must not be missed in antenatal period ***(Panchal et al., 2014).***

The fetal echocardiography examination emerged almost 40 years ago, and from the beginning it advocated that only the fetuses of pregnant women at high risk for CHD should undergo this examination. However over the years, it was observed that more than 90 % of CHD occurs in low risk population so CHD screening should be performed in all pregnant women ***(Began et al., 2001).***

Till now, by screening we meant looking at the 4 chambers view of the heart and taking on M-mood to looking for arrhythmias, 4 chamber view diagnoses only 50-60 % of cardiac anomalies and including out flow tract will diagnose up to 75 % ***(Mc Gahan et al., 2009).***

About 25 years ago, the significance of prenatal diagnosis of CHD was considered very important for the fetus and outcome of pregnancy, possibility of postnatal correction or lifesaving intervention and prediction of life quality of the newborn and the family ***(Ahmed, 2008).***

Important criterion for the screening method is its simplicity, good sensitivity and specificity, acceptability, reliability and low cost, and the U/S introduction and development in ANC meet these criterion ***(Odibo et al., 2006).***

Two-dimensional ultrasound [2D] is in routine use in nearly most hospitals and many physician clinics as it offers a lot of benefits compared to other medical imaging techniques. Ultrasonography offers unique qualities including real-time imaging, physiologic measurement, use of non-ionizing radiation, no known bio-effects in the diagnostic range while being non-invasive. Sonographic image quality has benefited from increasingly sophisticated computer technology ***(Schaapas, 2010)***.

2D Ultrasound is basically an axial image and 3D Ultrasound is a volume and 4D Ultrasound is a volume with time and the fifth dimension is how do you bring a level of workflow into ultrasound? And it is basically bordering on the sense of automation. 5D technology is a form of automation where you go through and do a scan and you get the results auto populated for you ***(Haar, 2015).***

AIM OF THE WORK

- **Research Question:-**

Is Fetal Intelligent Navigation Echocardiography (FINE) method a rapid, simple and automated method for fetal heart examination?

- **Research Hypothesis :-**

Alternative Hypothesis: FINE method is a novel, rapid, simple and automated method able to detect nine views of the heart?

- **Medical Application:-**

Introduction of easy and accurate way to perform fetal echocardiography

Chapter One

INCIDENCE AND RISK FACTORS

Incidence of Congenital Heart Diseases (CHD)

Congenital heart diseases affect nearly 1% of births per year in United States of America ***(Hoffman and Kaplan, 2002; Reller et al., 2008).*** Inclusion of a large number of premature neonates in a study may increase incidence of CHD as patent ductus arteriosus and ventricular septal defects are common in that group ***(Abuhamad and Chaoui, 2010). Hoffman and Christianson (1978)*** stated that congenital heart diseases account for more than 50% of deaths from congenital abnormality. About 25% of babies with congenital heart diseases have a critical CHD which generally need surgery or other procedures in their first year of life.

Hoffman and Christianson (1978) stated that 46% of CHD are diagnosed by 1st week of life, 88% are diagnosed by 1st year of life and 98% are diagnosed by 4th year of life.

Hoffman and Kaplan (2004) gave the incidence of CHD per 1000 live births according to type. They found that ventricular septal defects incidence was 3.57, atrial septal defects was 0.94, pulmonary stenosis incidence was 0.73, tetralogy of fallot incidence was 0.42, and coarctation of aorta was 0.41. They found also that aortic stenosis incidence was 0.46, complete transposition of the great arteries incidence was

0.31, hypoplastic left heart incidence was 0.22, double outlet right ventricle was 0.16, pulmonary atresia was 0.13 and Epstein anomaly was 0.114.

Risk Factors for Congenital Heart Diseases

Fetal Risk Factors:

Extracardiac anatomic abnormalities

Cunningham (2005) said that as many as 30-40% of cardiac defect diagnosed prenatally are associated with chromosomal abnormalities and fortunately up to 50-70% of aneuploidy fetuses have extra cardiac anomalies that are identified ultrasonographically. They added that the most frequently encountered aneuploidy are trisomies 21,18 and 13 and monosomy 45 X (turner syndrome), ***Abuhamad and Chaoui (2010)*** stated that the presence of extracardiac abnormalities in a fetus is frequently associated with CHD and is thus an indication of fetal echocardiograph. CHD is present in 10-20% of fetuses with non-immune hydrops ***(Friedman et al., 1993). Greenwood et al. (1976a)*** had reported the incidence of cardiovascular malformations with congenital abnormalities of renal system. They found CHD in 42% of cases of bilateral renal agenesis, 38.8% in cases with horse-shoe kidney, 16.9% with unilateral renal agenesis, and 5.4% in cases with renal dysplasia. Regarding abnormalities of gastrointestinal system. ***Fonkalsrud et al. (1969)*** reported that CHD were found in 17.1% of cases with duodenal atresia. ***Greenwood and***

Rosenthal (1976) found CHD in 14.7% of cases with tracheoesophageal fistula. ***Greenwood et al. (1975)*** found CHD in 11.7% of cases with imperforate anus, ***Delorimier et al. (1969)*** found CHD in 5.2% of cases with jejunal ileal atresia.

Other extracardiac anomalies that was diagnosed ultrasonographically may indicate presence of CHD, ***Burton (1979)*** found CHD in 4.4% of cases with isolated hydrocephalus. Beckwith-Wiedmann Syndrome cases have 92.3% incidence of CHD ***(Greenwood et al., 1977)***. CHD was found in 9.6% of cases with diaphragmatic hernia ***(Greenwood et al., 1976b). Greenwood et al. (1974)*** found CHD in 19.5% of cases with omphalocele. In 77.8% of cases with pentalogy of Cantrell, there was CHD ***(Toyoma, 1972).***

Thickened Nuchal Translucency (NT) Thickness

Measurements of fetal NT thickness in late 1st trimester of pregnancy is currently established as an effective method for individual risk assessment for fetal chromosomal bnormality ***(Abuhamad and Chaoui, 2010).*** An association between increased NT thickness and major fetal malformations including cardiovascular defects was noted by many reports ***(Soulka et al., 2001; Nicholaides 2004). Atzi et al. (2005)*** found a prevelance of 25/1000 pregnancies of CHD with NT > 3.5 mm in chromosomally normal fetuses. Fetal echocardiography with NT > 3.5 mm may lead to early diagnosis of all major types of CHD ***(Makrydimas et al., 2005). Bhado-Singh et al.***

(2005) found that prevelance of CHD with NT thickness > 3.5 mm was 23/1000 pregnancies compared to 1.9/1000 pregnancies with NT thickness < 2 mm, 4.8/1000 pregnancies with NT thickness 2-2.4 mm and 6/1000 pregnancies with NT thickness 2.5-3.4 mm.

Suspected Cardiac Anomalies

Suspicion for the presence of a cardiac abnormality during routine ultrasound examination is one of the highest yield for CHD ***(Crowford et al., 1988). Friedman et al. (1993)*** confirmed CHD in 40%-50% of pregnancies referred with finding of suspected cardiac anomalies.

Fetal Cardiac Arrhythmais

Abuhamad and Chaoui (2010) stated that the presence of cardiac arrhythmias may be associated with an underlying structure heart defects. ***Creasy and Resnik (1994)*** found that extrasystole had accounted for more than 90% of fetal cardiac arrhythmias. About 1% of fetal cardiac arrhythmias are associated with CHH ***(Friedman et al., 1993).*** However, presence of complete heart block was associated with structural heart defects in 50% of cases ***(Crowford et al., 1985).***

Monochorionic placenta

Manning an Archer (2006) found that overall risk of at least one of the twin pair has structural CHD was 9.1%. the

found that the risk was 57.1% in monochorionic monoamniotic twins. Compared to 7% in monochorionic diamniotic twins. They found also that if one twin is affected, the other twin is affected in 26% of cases. The increased risk for CHD was independent of TTTs ***(Bahtiyar et al., 2007).*** They found also that the VSD was the most common type of CHD in non TTTs fetuses compared to pulmonary stenosis and atrial septal defects which were more present in TTTs fetuses.

Maternal Risk Factors:

Diabetes mellitus

DM has a significant effect on the incidence of CHD. The incidence is fivefold higher in diabetic mothers compared to controls ***(Rowland et al., 1973).*** The incidence of major malformations in women with type I DM is about 5% ***(Shefield et al., 2002).*** Ventricular septal defects and transposition of great vessels are common in fetuses of diabetic mothers ***(Rowland et al., 1973).***

Good pre conceptional care leading to lower glycosylated haemoglobin in early pregnancy was associated with lower congenital anomalies ***(Miller et al., 1981; Yinen et al., 1984).***

Infants of diabetic mothers may have hypertrophic cardiomyopathy that occasionally progress to heart failure ***(Reller and Kaplan, 1988; Gandhi et al., 1995).*** Fetal hyperinsilinemia has been implicated in pathogenesis of heart

disease ***(Cunningham et al., 2005). Way et al. (1979),*** reported that the cardiomyopathy generally disappears in 6 months.

Fetal echocardiography should therefore be offered to all pregnancies with initial HBA1C above the upper limit of normal ***(Shields et al., 1993).***

Phenyl Ketonuria (PKU)

Another metabolic disorder that is associated with CHD is phenyl ketonuria. PKU patients usually follow unrestricted dietary regimen in adulthood ***(Abuhamad and Chaoui, 2010). Lenke and Levy (1980)*** reported that fetal exposure to phenylalanine levels > 15mg/dl is associated with 10 to 15 folds increase in CHD. With preconception counseling and adherence to phenylalanine restricted diet before pregnancy, the incidence of fetal malformation is dramatically reduced ***(Guttler et al., 1990; Koch et al., 1990).*** The PKU collaborative study evaluated the effectiveness of preconceptional care in preventing PKU related fetal defects, almost 300 women with PKU began a low phenylalanine diet preconceptionally. Zero percent had fetuses with cardiac defects compared to 16% in mothers with poor dietary control. The knowledge of the effect of PKU with pregnancy increased the proportion of women treated preconceptionally from 7% in 1984 to 51% in 1994 ***(Platt et al., 2000).***

Connective Tissue Diseases

Systemic lupus erythematous

Anti-ss-A (Ro) and anti-ss-B (La) antibodies may damage fetal heart and conduction system causing neonatal death ***(Tseng and Buyon, 1997). Buyon et al. (1993)*** reported that congenital heart block occurred most exclusively in infants of women with antibodies to ss-A or ss-B antigens. Even, in the presence of such antibodies, the incidence of arrhythmias is only 3% ***(Lockshin et al., 1988).*** The cardiac lesion is permanent and pacemaker is generally necessary. Long-term prognosis is not good and 1/3rd of the affected infants die within 3 years ***(Waltuck and Buyon, 1994).***

Teratogenic Drugs

Numerous drugs have been suspected as a cardiac teratogens Evidence suggests that overall contribution of teratogens to CHD is small ***(Tickanen and Heinonen, 1991).***

Cardiac defects, as a part of fetal hydantoin syndrome can occur due to phenytoin therapy, about 5-11% are affected ***(Cunningham et al., 2005). Hanson and Buechler (1982)*** noted incidence of congenital defect ranging from 2.2-26% with treatment by phenyl hydantoin in early pregnancy. Cardiac anomalies are common, with septal defects occurs in about 2% of fetuses exposed to phenyl hydantoin ***(Briggs et al., 1994).*** The fetal hydantoin syndrome can occur with carbamizine treatment

(Abuhamad and Chaoui, 2010). Cardiac defects can also occur due to treatment with phenobarbitone or trimethadone in early pregnancy. Although some reports have suggested an increased risk of CHD in fetuses exposed to valproic acid ***(Thisted and Ebesen, 1993),*** others could not establish a causal relationships ***(Lindhout and Meinardi, 1984).***

Ethinyl alchol is one of the most potent teratogens ***(Cunningham et al., 2005). Sidhu and Floyd (2002)*** noted an average use of 12.8% during pregnancy in united states.

The features of fetal alcohol syndromes according to ***Cunningham et al. (2005)*** includes behavioral changes, brain defects, spinal defects, craniofacial anomalies and cardiac defects. CHD has been identified in 25-30% of infants with fetal alcohol syndrome, with septal defects representing the most common lesion ***(Clarren and Smith, 1978).***

Reports initially suggested an association between maternal lithium exposure and development of Ebstein anomaly ***(Schou et al., 1973).*** Subsequent studies found that lithium is not a major teratogen ***(Cohen et al., 1994).*** The teratogen risk of lithium exposure is lower than previously reported and that the risk/benefits ratio of prescribing lithium in pregnancy should be evaluated in light of the modified risk estimate ***(Abuhamad and Chaoui, 2010).*** It would see prudent to avoid lithium exposure until at least 6-8 weeks gestation when organogenesis is completed and cardiac structures have formed ***(Briggs et al., 2002).***

Indomethacin and other non-steroidal anti-inflammatory drugs causes constriction of ductus arteriosus in sheep and human fetuses ***(Huhta et al., 1987).*** In a study of 61 indomethacin pregnant women, ***Vermillon et al. (1997)*** reported that half of exposed fetuses developed ductal constriction. Fortunately, this complication is largely reversible if medication is discontinued before 32 weeks ***(Moise, 1993). Norton et al. (1993)*** stated that there was a risk of patent ductus arteriosus requiring surgical ligation in indomethacin exposed infants.

Angiotensin-Converting Enzyme (ACE) inhibitors which were used as antihypertensive agents have been associated with many reports of fetal damage ***(Cunningham et al., 2005). Cooper et al. (2006)*** found that fetal exposure to ACE inhibitors in the first trimester of pregnancy had been associated with an increased risk of major congenital malformations primarily affected cardiac system (risk ratio 3.72). They added that atrial and ventricular septal defects represented the most cardiac abnormalities.

The most commonly used anti-depressants are the selective serotonin reuptake inhibitors and these agents are a good choice of pregnant women as they have fewer side effects compared to other antidepressant ***(Cunningham et al., 2005). Cole et al. (2006)*** found that fetuses exposed to SSRIs in 1st trimester had shown an increased risk of CHD. Paroxetine has been singled out as the SSRIs with the greatest association with congenital heart malformations, primarily atrial and ventricular septal defects ***(Abuhamad and Chaoui, 2010).*** A meta-analysis

of seven studies noted a significant overall increased risk of 74% for CHD in fetuses exposed to paroxetine in 1st trimester of pregnancy ***(Bar-oz et al., 2007).*** U.S. food and drug administration (2007) issued a warning against use of paroxetine in 1st trimester of pregnancy. The use of other SSRIs should be individualized. Doctors and their patients must weigh both the benefits and potential risks of SRRIs treatment in the context of the risk of recurrence of depression if maintenance therapy is discontinued ***(Abuhammad and Chaoui, 2010).***

Viral infections

Viral infections in pregnancy are major causes of maternal and fetal morbidity and mortality. Infections can develop in the neonate transplacentally, perinatally (from vaginal secretions or blood), or postnatally (from breast milk or other sources). The clinical manifestations of neonatal infections vary depending on the viral agent and gestational age at exposure. The risk of infection is usually inversely related to gestational age at acquisition, some resulting in a congenital malformation syndrome.

Infections known to produce congenital defects have been described with the acronym TORCH (Toxoplasma, others, rubella, cytomegalovirus [CMV], herpes). The "others" category has rapidly expanded to include several viruses known to cause neonatal disease.

Traditionally, the only viral infections of concern during pregnancy were those caused by rubella virus, CMV, and herpes simplex virus (HSV). Other viruses now known to cause congenital infections include parvovirus B19 (B19V), varicella-zoster virus (VZV), West Nile virus, measles virus, enteroviruses, adenovirus, and human immunodeficiency virus (HIV).

Rubella

Rubella is one of the most teratogenic viruses. Congenital rubella syndrome (CRS) is characterized by intrauterine growth restriction, intracranial calcifications, microcephaly, cataracts, cardiac defects (most commonly patent ductus arteriosus or pulmonary arterial hypoplasia), neurologic disease (with a broad range of presentations, from behavior disorders to meningoencephalitis), osteitis, and hepatosplenomegaly.

Heart defects in these infants include ventricular septal defects, patent ductus arteriosus, pulmonary stenosis, and coarctation of the aorta ***(Miller et al., 1982).***

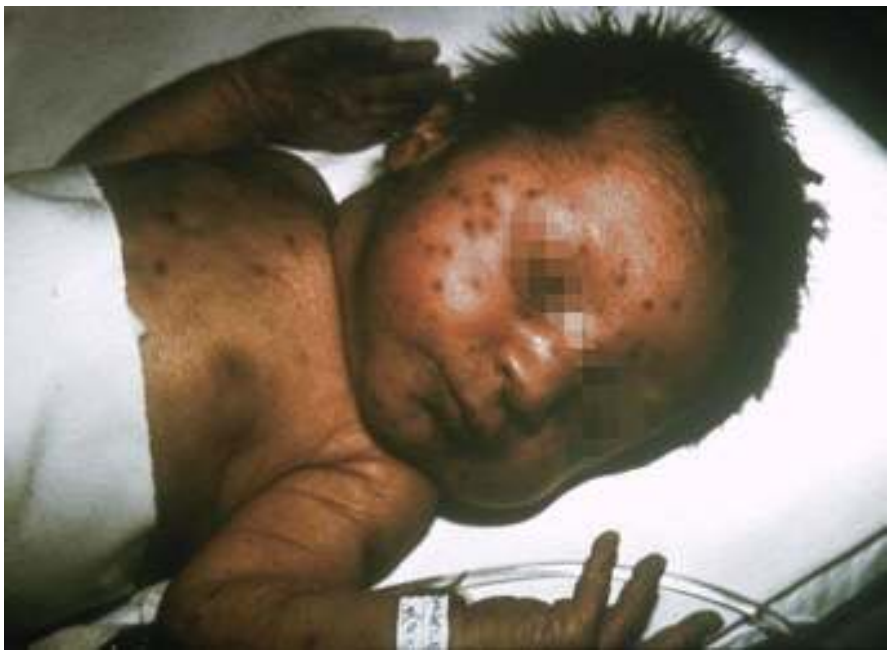

Fig. (1): Infant with congenital rubella syndrome.