ORIGINAL ARTICLE

PRETERM DETECTION OF CONGENITAL ANOMALIES BY ULTRASOUND AND CORRELATION WITH POSSIBLE ASSOCIATED RISK FACTORS

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ABSTRACT

The aim: This descriptive, cross-sectional study aims to determine the prevalence of congenital anomalies in the Iraqi population, the associated risk factors & to emphasize the importance of ultrasound examination during pregnancy especially in the high-risk group.

Materials and methods: Data were collected from three private ultrasound clinics in different areas in Baghdad, where many pregnant women were examined over one year and those who had abnormal fetus were questioned about any possible risk factor.

Results: The study revealed a prevalence of (14/1000). The most common anomalies are those related to the central nervous system. Some of the patients had no risk factors, others had one or more, the most important of which was consanguinity.

Conclusions: The prevalence of congenital anomaly had both geographical and temporal variations, but in general, it was increasing with time and became relatively higher in the middle and south of Iraq compared with the north. This may be related to differences in ethnic, social and demographic factors as well as environmental factors, like pollution and war residues. Ultrasound had a valuable role in screening, detection and follow-up of congenital anomalies. It is a safe, available and cost-effective examination that should be offered to every pregnant woman, especially those with high-risk pregnancies.

KEY WORDS: congenital anomalies, ultrasound, risk factors

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INTRODUCTION

In the past, the diagnosis of congenital anomalies was primarily dependent on amniocentesis and chorionic villi sampling [1]. In the last 2 decades, the advances in ultrasound technology led to substantive improvement in the early detection of such anomalies [2]. Ultrasound plays an important role, not only in the primary detection of structural anomalies but also as guidance of amniocentesis needles or chorionic villous sampling catheters to take genetic material for analysis [3].

Congenital anomalies can be defined as structural or functional defects developed during the intrauterine life; they can be detected prenatally, after birth, or later, after causing deaths, chronic illness, or disability [3].

The global birth prevalence of congenital anomalies is about 2-3% [4,5]. i.e. the prevalence is 20 – 30/1000 live birth in the neonatal period; however, some defects are not recognizable at this early age and may be detected later so that the prevalence is increased to 40 – 80/1000 in the first 5 years of life i.e. 4 – 8 % [5].

Despite in 50% of all congenital anomalies no specific cause could be identified, there are some known genetic, environmental, or their combination as multifactorial causes or risk factors [3].

Firstly, there are genetic causes, including chromosomal abnormalities and single gene abnormalities. Chromosomes are packages of DNA that carry genetic material from one generation to the next. The human somatic cell has 46 chromosomes arraigned in 23 pairs: 22 pairs called autosomes and one pair of sex chromosomes (XX in a female and XY in a male), one in each pair is from the mother and aother - from the father i.e. 22 autosomes and X chromosome from the mother (in the ova or the egg) and 22 autosomes plus X or Y chromosome from the father (in the sperm) which determines the gender. [5, 6] Chromosomal anomalies may be numerical or structural [4].

Numerical chromosomal anomalies occur when there is an extra chromosome from the egg or the sperm in the fetus which may develop serious health problems (e.g. Down

syndrome or trisomy 21, in which there are 3 copies of chromosome 21 instead of 2, with a total of 47 chromosomes in each cell instead of 46). Other similar but less common conditions are trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome), trisomy X (XXX) when there is an extra X chromosome in a female; or Klinefelter syndrome (XXY) when there is an extra X chromosome in a male. [5,6] Less commonly, there are conditions in which there is a missing chromosome like Turner syndrome (X0) in which there is a missing X chromosome in a female with a total of 45 chromosomes in each cell instead of 46 [5,6].

Structural chromosomal anomalies occur when there is a defect in the structure of a chromosome such as deletion, duplication, insertion, or translocation of segments of the chromosome [4].

Single-Gene abnormalities occur when the number of the chromosomes is normal, but one or more of the genes are abnormal. Gene may become abnormal by mutation which occurs spontaneously or is caused by certain environmental factors, e.g. radiation. The abnormal gene can be inherited as:

Autosomal dominant inheritance**:** the child may be affected if one of the parents has the abnormality (e.g. neurofibromatosis type I and/or adult onset polycystic kidney disease). The gene can also appear for the first time in a person of normal parents as a result of a new mutation. However, the new gene will be inherited by his children as an autosomal dominant gene [5,6].

Autosomal recessive inheritance: the gene is weak, so the child is only affected if both parents have the abnormality. In such a condition, both parents are normal, but 25 % of their children can be affected. A person that carries a 'hidden' recessive gene is called a carrier (e.g. neurofibromatosis type II and pediatric-onset polycystic kidney disease) [5,6].

X-linked conditions mainly affect males (e.g. hemophilia, color blindness). Females can have the abnormal gene, but not have the actual disease [5,6].

X-linked dominant conditions affect both males and females and are more severe in males (e.g. Certain types of skeletal disorders) [5,6].

Therefore, consanguinity (i.e. parents related by blood) is associated with increased prevalence of rare genetic congenital anomalies and higher risk for neonatal and childhood death or disability. Advanced maternal age also increases the risk of chromosomal abnormalities, e.g. Down syndrome [3].

Secondly, there are environmental conditions that affect the fetus during pregnancy, e.g. maternal illness like diabetes which may increase the risk of congenital anomalies by 2 – 3 folds and is inversely related to good maternal control [4]. Maternal hypertension and some autoimmune diseases may affect blood flow to the placenta and the fetus; and, therefore, affect fetal growth [6].

Maternal nutritional status: e.g. folate insufficiency, increases the incidence of neural tube defects. On the other hand, excessive intake of vitamin A may also affect the normal development of an embryo or fetus [3].

Infections, like cytomegalovirus, herpes virus, rubella, toxoplasmosis and syphilis are associated with significant congenital anomalies [3,4].

Chemical agents including certain drugs, alcohol, tobacco, cocaine, and radiation during early pregnancy can increase the risk of having a baby with congenital anomalies [3,4].

Mechanical causes, e.g. oligohydramnios, amniotic bands, uterine tumors and malformations may cause mechanical compression of the developing fetus resulting in certain deformities [4,5].

Socioeconomic factors are indirect determinants with a higher risk of congenital anomalies being related to lack of nutrition, increased exposure to infection and pollution, or poor access to medical care and screening [3].

Thirdly, multifactorial causes are a combination of both genetic and environmental factors [5].

Ultrasound is the modality of choice for the screening and detection of congenital anomalies as it is non-invasive, safe, sensitive and cost-effective. Prenatal diagnosis of congenital anomalies allows for proper decisions, fetal intervention if possible and appropriate treatment as well as timed delivery in specialized centers, consequently, improves perinatal and long-term results [7].

Ultrasound screening in the first trimester between 10-14 weeks of gestation should include the measurement of nuchal translucency (the maximum thickness of the translucency between the skin and the soft tissue of the neck of the fetus). Nuchal translucency of more than 3 mm is associated with chromosomal and structural anomalies especially cardiac malformations [8].

Second-trimester ultrasound can detect chromosomal anomalies (especially Down syndrome) base on certain "soft markers" (e.g., ventriculomegaly, choroids plexus cysts, large nuchal fold, echogenic intracardiac focus, echogenic bowel, pyelectasis, short femur, and humorous), however, the validity of those markers as indicators of chromosomal anomalies is controversial. Also, these "Down syndrome markers" include common findings seen sometimes in normal fetuses (e.g. echogenic intracardiac focus can be seen in about 5% of normal fetuses). Therefore, although ultrasound soft markers allow increasing of congenital anomalies detection; it can lead to a big increase in false positives. However, the detection of one marker warrants careful scanning to detect additional markers as the finding of multiple markers means a high risk of chromosomal anomaly [8].

Most structural anomalies can be increasingly detected in advancing gestation. Some anomalies can be detected with confidence in early pregnancy, like anencephaly, which can be recognized at 10-14 weeks of gestation. Other anomalies like urinary tract anomalies can only be detected in later pregnancy. Ultrasound screening of structural abnormalities is usually recommended at 19-21 weeks of gestation [8].

The accuracy of ultrasound results, therefore, depends on gestational age. Other factors that affect sensitivity include the type of malformation (major or minor, single or multiple, natural progression during fetal life), in addition, there is large variability between centers and operators [8].

THE AIM

1. To emphasize the importance of ultrasound examination during pregnancy especially in high-risk groups.
2. To find out the prevalence of congenital anomalies in our population.
3. To delineate the associated causes and risk factors.

MATERIALS AND METHODS

This is a descriptive, cross-sectional study performed in 3 private ultrasound clinics in Baghdad, including 5142 pregnant women who attended those clinics in one year from 1st of October 2019 to the 30th of September 2020, from whom 72 women were having abnormal babies. A special questionnaire form was used for the collection of data using direct interview and included the following information: maternal age, consanguinity, any illness presence, drugs, chemicals and/or radiation exposure. All those women went through laboratory tests for toxoplasmosis, cytomegalovirus and rubella virus.

RESULTS

There were 72 cases of single or multiple congenital anomalies out of 5142 pregnancies examined in one year (prevalence = 14/1000), there were 42 male fetuses (58.3%) and 30 were females (41.7%).

The central nervous system is the most commonly affected system (29.2%) 21 patients were affected, 6 of which had anencephaly per se, 5 had hydrocephalus, 4 had spina bifida and meningocele, 3 patients had anencephaly with spina bifida and meningocele, and 3 had choroid plexus cyst as a soft marker that may be associated with chromosomal abnormalities.

The urinary system was the second commonly affected system (26.4%) 19 patients were affected, 5 of which had autosomal recessive polycystic kidney disease; 3 had unilateral pelvi – ureteric junction obstruction with unilateral hydronephrosis; 2 had bilateral pelvi – ureteric junction obstruction with bilateral hydronephrosis; 3 had posterior urethral valve with distended urinary bladder, bilateral hydroureters and hydronephrosis; 2 had empty urinary bladders with bilateral hydroureters and hydronephrosis suggesting vesicoureteric reflux or primary megaureters; 1 had a unilateral duplicated kidney, 1 had single Lt kidney, 1 had horseshoe kidney and 1 had ectopia vesicae.

The digestive system was affected in (12.5%), 4 patients had diaphragmatic hernia, 2 patients had signs of bowel obstruction, 1 had absent gastric babble which suggest esophageal atresia, 1 had double babble sign of duodenal atresia and 1 patient had omphalocele.

Nine patients (12.5%) had nuchal translucency of more than (3 mm) suggesting possible chromosomal or structural anomalies, 5 of them were proved to have Downs syndrome after delivery, 8 patients (11.1%) had cystic hygroma, 6 patients (8.3%) had cleft lip and palate. Results are illustrated in table I.

Table I. Anomaly, Number and Percentage

Anomaly	Number	percentage
Central nervous system	21	29.2%
Urinary system	19	26.4%
Digestive system	9	12.5%
Increased nuchal translucency	9	12.5%
Cystic hygroma	8	11.1%
Cleft lip +/- palate	6	8.3%
total	72	100%

The p-value is a statistical measure that helps scientists determine whether a certain hypothesis is correct or not. The probability value is used to determine whether the results of an experiment are within the normal range of values for the subject of research. Usually, if the probability value of a data set is less than a certain predetermined amount (say: 0.05), then scientists reject the "null hypothesis" of the experiment - that is, they exclude the hypothesis that the experiment's variables did not have a significant effect on the results. Today, you can access the different probability values by looking at

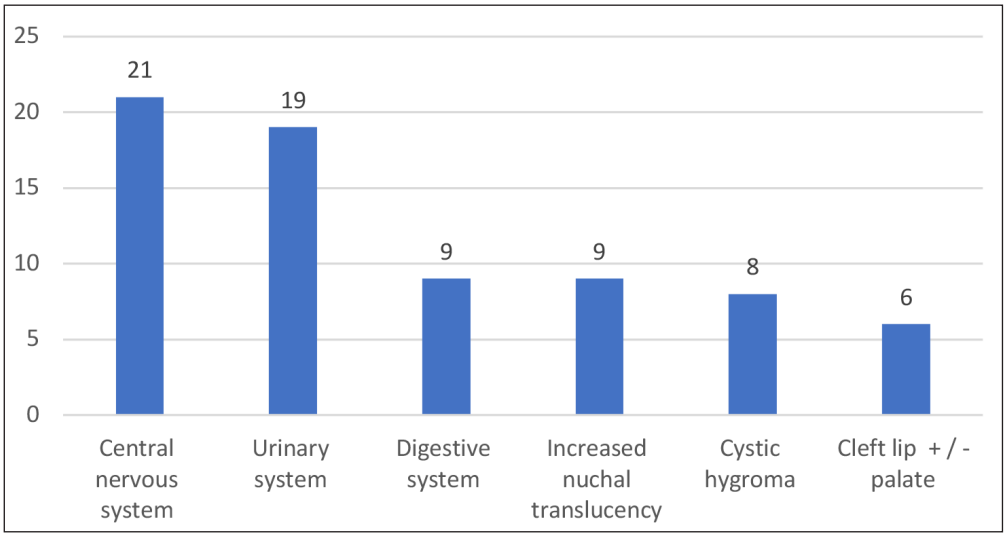

Fig. 1. Numbers of Anomalies

Table II. One-Sample Statistics of Anomalies

	N	Mean	Std. Deviation	Std. Error Mean
X	6	12.0000	6.32456	2.58199

Table III. One-Sample Test of Anomalies

	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
X	4.648	5	.006	12.00000	5.3628	18.6372

Table IV. Factors, Number and Percentage

Factors	Number	percentage
Maternal age > 35 y	9	12.5 %
Consanguinity	15	20.8 %
Diabetes	4	5.6 %
Hypertension	3	4.2 %
Infection	6	8.3 %
Drugs	5	6.9 %
Smoking	6	8.3 %
Radiation	1	1.4%
Total	49	68%

Table V. One-Sample Statistics of Factors

	N	Mean	Std. Deviation	Std. Error Mean
x	8	6.1250	4.29077	1.51702

the tables for the values of choice (t) as well as the chi-square, which are called tabular values, which are compared with the extracted value, and in light of this, the two hypotheses of Null Hypothesis and Alternative Hypothesis.

Using the (SPSS) program, and from table I above, it was found that the mean of the data values is (12) with a standard deviation of (6.32456) according to table II.

As shown in table III, the value of (t) test was (4.648) in terms of (0.006), which is much less than (0.05) and since the extracted value for the test is greater than the tabular value of (2.015) for the degree of freedom (5), i.e. the alternative hypothesis is accepted and the null hypothesis is rejected.

The form of the spread of the sample data above can be illustrated in figure 1.

Correlated factors, as illustrated in table IV.

1. Maternal age: the age of the 72 women who had abnormal babies ranged from 14 – 45 years, only 9 of them (12.5%) were above 35 years.

2. Consanguinity: 15 patients (20.8%) were blood-related with their husbands, 4 of which had positive family history of congenital anomalies; another 2 patients had affected babies before.

3. Most of the patients are healthy, only 4 had diabetes; 3 had hypertension.

4. Three patients had positive tests for cytomegalovirus, two patients had positive tests for toxoplasmosis; 1 had rubella.

Table VI. One-Sample Test of Factors

	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
x	4.038	7	.005	6.12500	2.5378	9.7122

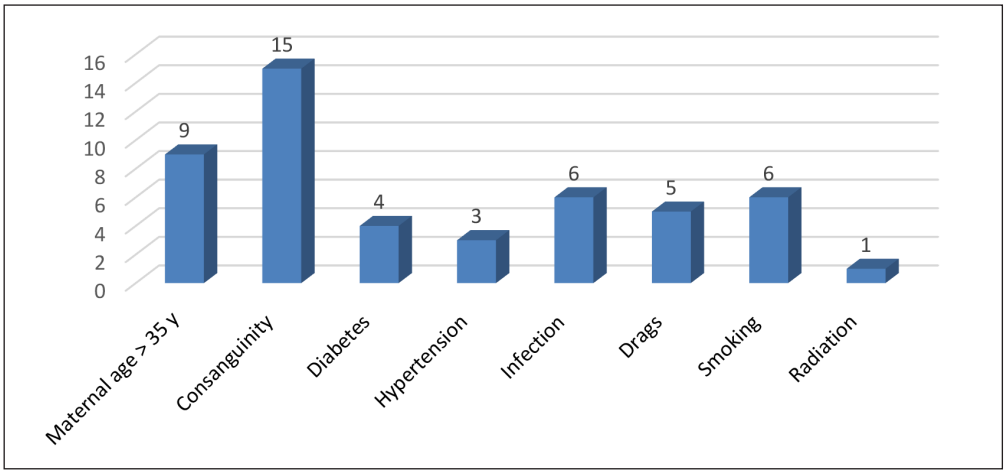

Figure 2. Numbers of Factors

5. Six patients were smokers, 5 patients had history of debatable drug consumption, none had a history of alcohol consumption

6. One of the patients suffered the radiation exposure during pregnancy.

Using the (SPSS) program, and from table IV above, it was found that the mean of the data values is (6.1250) with a standard deviation of (4.29077) according to table V.

As shown in table VI, the value of (t) test was (4.038) in terms of (0.005), which is much less than (0.05), since the extracted value for the test is greater than the tabular value of (1.895) for the degree of freedom (7), meaning that the alternative hypothesis is accepted and the null hypothesis is rejected.

The form of the spread of the sample data above can be illustrated in figure 2.

DISCUSSION

The prevalence of congenital anomalies in our study (14/1000) is relatively high when compared with (12.36/1000) reported in Baghdad in 2007 [9].

Similarly, there is increasing prevalence reported by studies from Al-Anbar which revealed a value of (8.5/1000) in 2002 [9] increased to (48/1000) in 2009 [10] and to a significantly high prevalence of (84/1000) reported in 2013 [11].

In Basrah, the prevalence of birth defects was (3.04/1000) in 1990, increased to (7.76/1000) in 1998 then to (13.49/1000) in the period 1999–2000 [9].

A study in Mosul city reported a prevalence of (6.9/1000) for the period from January/2009 to December/2010. [12] While a slightly higher prevalence was reported (7.1/1000) by a study conducted from October/2017 to October/2018 [13].

Studies carried out in Kurdistan showed a prevalence of (3.06/1000) in Erbil, between 2004-2005 [14], which was slightly increased to (3.63/1000) in 2015-2016. [15] A similar figure was recorded in Sulaimaniyah where a study published in 2018 showed that the prevalence of congenital anomalies was (3.3/1000) [16].

It is clearly noticed that there are wide geographical and temporal variations in the prevalence of congenital anomalies in different areas of Iraq but in general, the prevalence is higher in the middle and south regions compared with the north cities; meaning there are progressively higher figures over time.

There is slight male predominance noticed in our studies. Similar results were seen in some of the studies mentioned above [10, 14] other studies showed a slight female predominance [12, 13]; therefore, the role of fetal gender seems to be controversial.

The central nervous system is the most common involved system in our study (29.2%) as well as in most of the studies mentioned above [9, 12-16].

No associated risk factor was found in (32%) of our patients, however, there was at least one factor in (68%) of our patients. Consanguinity (blood-related parents) was the leading factor in our study (20.8%) as well as some other studies [10,12,15,17] as it increases the possibility of inheritance of abnormal genes [3]. Studies showed that the rate of congenital anomalies is 2.5 times higher in the offspring of consanguineous marriages than that in the offspring of unrelated parents, mostly resulting from the expression of autosomal recessive disorders [18].

Other factors include advanced maternal age (12.5%) as it may increase the possibility of numerical chromosomal anomalies, especially Down's syndrome [3]. Although there is a clear association between chromosomal anomalies and advanced maternal age, there are still debates about structural anomalies, however, anomalies like neural tube defect, congenital hernia and cleft lip or palate, are more prevalent with advanced maternal age. [19]

Maternal diabetes was an attributing factor in (5.6%) of our sample. It is well known that maternal diabetes may have toxic effects on the fetus and may increase the risk of congenital anomalies. Pregestational diabetes may increase the incidence of fetal structural anomalies by three to fourfold. The congenital anomalies associated with maternal diabetes usually arise before the seventh week of gestation. It may affect any system, like the central nervous system (CNS), including neural tube defect as anencephaly, spina bifida & other malformation like holoprosencephaly or microcephaly; the skeletal system may also be affected in form of limb maldevelopment, vertebral segmentation defect, sacral agenesis and caudal regression syndrome; the renal system can be affected, this includes anomalies like renal agenesis, ureteric obstruction and hydronephrosis; cardiac defects like atrial septal defects, ventricular septal defects, transposition of the great vessels and coarctation of the aorta; and anomalies of the gastrointestinal system including duodenal atresia, microcolon and rectal or anal atresia also had higher incidence in association with maternal diabetes. Regular counseling of diabetic pregnant women with good metabolic control may decrease birth defects [20].

Maternal teratogenic infection was an association in (8.3%), particularly cytomegalovirus, toxoplasmosis and rubella. Most of these pathogens have asymptomatic or mild maternal illnesses but have serious impacts on the fetus, like congenital anomalies, intrauterine growth retardation, abortions and stillbirths, premature labor, and chronic postnatal illness [21]. Cytomegalovirus differs from toxoplasmosis and rubella, which can cause congenital malformations only if the maternal infection occurred shortly before or during the pregnancy. CMV, on the other hand, can affect the fetus even if the maternal infection occurred months or years before pregnancy [22].

Maternal hypertension was an associated factor in (4.2%) of our study. In addition to the fact that maternal hypertension may affect fetoplacental circulation and, therefore, have an adverse effect on fetal growth that may result in low birth weight, [6] there is also an association with congenital malformation. The association between pregnancy-induced hypertension (preeclampsia/ eclampsia) & congenital malformation is weak, presumably because of different times of onset of those two events, as most congenital anomalies occur in the first trimester

while pregnancy-induced hypertension usually occurs in a later time of gestation. However, the association between pregnancy-induced hypertension and congenital heart anomalies is certain [23].

Pregnant mothers with chronic hypertension apparently had the condition before and throughout pregnancy including the critical period of organogenesis at which most congenital anomalies develop. Studies showed that there is an increased risk of renal, limb, cleft lip/palate malformations in association with chronic maternal hypertension especially those with superimposed preeclampsia/ eclampsia. Some studies showed increased risk of esophageal stenosis/ atresia, rectal/ anal stenosis/atresia and hypospadias in association with chronic maternal hypertension alone or with superimposed preeclampsia. There were also debates about a similar association with neural tube defects. In addition, the teratogenic effect of antihypertensive drugs is still debatable [23].

Smoking was an association in (8.3%) of our patients. Smoking during the initial growth period of pregnancy may have an adverse impact on the fetus. There is an increased risk, not only of spontaneous abortion, placental abruption, and intrauterine growth restriction but in addition, there is a higher rate of congenital malformation including cleft lip/ palate, skull and limb deformities, renal and cardiac anomalies defects. There are also debates about a higher incidence of Down syndrome. These anomalies probably result from hypoxia and carboxyhemoglobinemia caused by smoking and are also seen in association with CO poisonings [24].

Intrauterine exposure to certain toxicants, especially in the early phase of pregnancy, can cause many congenital malformations and even fetal death. Teratogenic agents include physical agents like ionizing radiations, chemical agents and a list of many medical or pharmacological agents, for example, thalidomide which used to be prescribed to relieve morning sickness linked with early pregnancy before it was found to have considerable teratogenic effect in the 1960s. Other drugs including Vitamin A, some anticonvulsants, antihypertensives, anticoagulants, corticosteroids, antimalarial, antileishmaniasis, antimycotic and some antibiotics also have certain teratogenic effects on the developing embryo. [25] Some of these drugs are implicated in (6.9%) of our patients & radiation in (1.4%).

CONCLUSIONS

The prevalence of congenital anomaly had both geographical and temporal variations, but in general, it was increasing with time. It was relatively higher in the middle and south of Iraq compared with the north; this may be related to differences in ethnic, social and demographic factors as well as environmental factors, like pollution, war residues.

The most common anomalies were those related to the central nervous system. Many anomalies had no associated risk factors, others had one or more predisposing factors the most important of which was consanguinity.

Ultrasound had a valuable role in screening, detection and follow-up of congenital anomalies. It is a safe, available, cost-effective examination that should be offered to every pregnant woman, especially those with high-risk pregnancies.

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