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DIAGNOSIS AND OUTCOME OF ANTENATAL OSTEOGENESIS IMPERFECTA – A GLOBAL META-ANALYSIS

Orthopaedics

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ABSTRACT

Objectives: Osteogenesis imperfecta (OI) encompasses a variety of heterogeneous conditions of connective tissue. Current study aims to determine accuracy of Ultrasonography (USG) for prenatal diagnosis and its impact on postnatal outcome of pregnancy. **Method:** Publicly available English databases, PubMed, Cochrane library and Google Scholar, were queried and mined a total of 164 research documents, of which 11 articles were selected based on predetermined criteria. The review analyzed protocol of scan, average gestational age, accuracy of diagnosis, diagnostic criteria, other investigation employed and conclusion of study. **Result:** Total 106 cases identified in studies, out of which 83 diagnosed correctly on prenatal USG. Out of these 83 cases 50 cases opt for Termination of Pregnancy (TOP), while 15 had perinatal mortality and 18 had live birth including 3 Cesarean sections (CS). Most of study employed detailed 2nd trimester scan. Diagnostic criteria in most study include shortening and bowing of long bones, hypomineralization of bones, multiple bone fractures including beaded ribs, oligohydramnios, chest hypoplasia and poor mineralization of calvaria. **Conclusion:** Detail 2nd trimester USG scan is investigation of choice. Findings of shortening and bowing of long bones, hypomineralization of bones and multiple bone fractures including beaded ribs is most accurate and commonly employed. Accurate diagnosis has great impact on genetic counselling of parents and their decision-making regarding continuation of pregnancy.

KEYWORDS

Osteogenesis Imperfecta, Prenatal or Antenatal diagnosis, Ultrasonography, Birth outcome

1. INTRODUCTION

Osteochondrodysplasias (OCD) are a heterogeneous group of rare genetic diseases that affect the growth and development of both bone and cartilage.[1] According to a recent study, OI was the second most common disorder.[2]

OI encompasses a variety of heterogeneous conditions of connective tissue whose main characteristic is fragile, brittle bones. There is a wide variation in severity between cases, the clinical course varying from death in the neonatal period to occasional fractures, deafness, and a normal lifespan. Based on clinical presentation and typical X-ray findings, OI can be divided into types I, II, III, and IV, type II being subdivided into types A, B, and C.[3,4,5,6]

Type II is always very severe and usually perinatally lethal, subtype: A being the most common form of perinatally lethal OI.[7] Type III OI may be a cause of neonatal death, but usually leads to progressive disability and death in childhood. Prenatal diagnosis may allow early diagnosis and termination of such fetuses, but it needs to be carried out during routine ultrasound screening as most women with an affected fetus have no relevant history.[3]

Second trimester ultrasound can detect congenital anomalies and reveals structural anomalies in ~1% of fetuses.[8] Detection is important for a number of reasons. In the short-term, it may provide a prognosis that allows parents to make better informed choices about continuing or terminating the pregnancy (termination is legally possible in the India until 24 weeks gestational age and is possible after this time under exceptional circumstances). In the medium-term, a prognosis can help the obstetrician determine the best obstetric management (e.g. delivery mode) and assist neonatologists in optimizing neonatal care. In the long-term, identifying the underlying genetic cause for an ultrasound anomaly is crucial for determining recurrence risk.[9]

The high-resolution ultrasound equipment, especially transvaginal (TVS) allows detailed visualization of fetal anatomy including specific anatomic landmarks and characteristics of normal ossification from early pregnancy.[10-15] Ossification centres, appearing as areas of increased echogenicity of the bone, can be recognized from 9 weeks onwards.[16] The prenatal ultrasonographic findings of type II are a compressible thin calvaria (which at sonography is transparent), severe shortening and bowing of the long bones, with multiple fractures, and a narrow thorax associated with multiple rib fractures.[17]

2. Materials and Methods:

2.1. Literature Search

Using PRISMA- systematic review and meta-analysis guidelines, the present study search to evaluate the effectiveness of prenatal ultrasound for diagnosis of OI and its impact on outcome of these patients was conducted. The inclusion criteria for screening include randomized, cohort and observational studies to understand the effectiveness of prenatal ultrasound diagnosis of OI and its association and impact on outcome. The exclusive criteria include review articles, study involving intervention and case reports. Literature searches are done in English databases such as PubMed, Cochrane library and Google Scholar. Time period for search was from 1980 to 2024. The main keywords for PubMed are osteogenesis imperfecta, prenatal diagnosis, antenatal diagnosis, antenatal ultrasound, skeletal dysplasia. The pertinent medical subject headings (MeSH) used are ("Osteogenesis Imperfecta" [Mesh] AND "Antenatal" [Mesh] OR "Prenatal" [Mesh] AND "Diagnosis" [Mesh] AND "Result" [Mesh] OR "Outcome" [Mesh] OR "Consequence" [Mesh]). To find other related studies, we thoroughly reviewed our options, selected the study with larger sample size or the most recent publication for our research samples, and then looked further into the publications' references to find comparable studies.

2.2. Selection and Screening

The screening approach consists of research articles performed separately by two researchers. Research documents were screened in the first step based on the title and abstract. Based on selection criteria, documents were thoroughly reviewed and articles not meeting the inclusion criteria were excluded from the study. Finally, the researcher independently retrieved pertinent data from the included studies using a pre-designed data-collecting form. Any differences in the data collected were sorted out through discussion. The primary contents of

the data collection form include the title of the research article, author name, year of publication, study design, indication, sample size, study population, methodology, Gestational age at diagnosis, Family History, Number of USGs done, whether any other additional investigations done, outcomes and conclusion of the study.

2.3. ROB Analysis

ROB analysis was done using ROBINS-2 (Risk of Bias in Nonrandomized Studies- version 2) of Cochrane tools. The subsequent domains were addressed to evaluate the bias.

- Domain 1: Risk of bias due to confounding
- Domain 2: Risk of bias in classification of interventions
- Domain 3: Risk of bias in selection of participants into the study (or into the analysis)
- Domain 4: Risk of bias due to deviations from intended interventions
- Domain 5: Risk of bias due to missing data
- Domain 6: Risk of bias arising from measurement of the outcome
- Domain 7: Risk of bias in selection of the reported result

The overall risk of bias for each domain was rated as Low risk, Moderate risk, Serious risk, Critical risk and No information.

Rating of each study for each domain described in table 1.

Table 1: ROB Analysis

Sr. No.	Article name	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Domain 7	Total Bias
1	Familial diseases revealed by a fetal anomaly. R Robyr et al.	Low	Low	Low	Low	Low	Low	Low	Low
2	Prenatal diagnosis of fetal skeletal dysplasia using 3-dimensional computed tomography: a prospective study. Waratani et al.	Moderate	Low	Low	Low	Low	Low	Low	Low
3	Prenatal diagnosis of fetal skeletal dysplasias by combining two-dimensional and three-dimensional ultrasound and intrauterine three-dimensional helical computer tomography. R Ruano et al.	Moderate	Low	Low	Low	Low	Low	Low	Low
4	Rapid prenatal diagnosis of skeletal dysplasia using medical trio exome sequencing: Benefit for prenatal counselling and pregnancy management. Han et al.	Low	Low	Low	Low	Low	Low	Low	Low
5	Diagnosis of fetal osteogenesis imperfecta by multidisciplinary assessment: a retrospective study of 10 cases. Wu et al.	Low	Low	Low	Low	Low	Low	Low	Low
6	Antenatal diagnosis of lethal skeletal dysplasias. Tretter et al.	Low	Low	Low	Low	Low	Low	Low	Low
7	Analysis of skeletal dysplasias in the Utah population. Stevenson et al.	Low	Low	Low	Low	Low	Low	Low	Low
8	Can transvaginal fetal biometry be considered a useful tool for early detection of skeletal dysplasias in high-risk patients? Gabrielli et al.	Low	Low	Low	Low	Low	Low	Low	Low
9	Prediction of lethal pulmonary hypoplasia by means fetal lung volume in skeletal dysplasias: a three-dimensional ultrasound assessment Barros et al.	Low	Low	Low	Low	Low	Low	Low	Low
10	Prenatal diagnosis of severe osteogenesis imperfecta. Constantine et al.	Moderate	Low	Low	Low	Low	Low	Low	Low
11	Prenatal diagnosis of osteogenesis imperfecta type II. Tongsong et al	Low	Low	Low	Low	Low	Low	Low	Low

3. RESULTS:

3.1. Literature Search and Study Characteristics

A summary of the systemic review search strategy with inclusion and exclusion articles was presented in a flowchart (Figure 1).

Table 2 shows the study characteristics of the selected studie

Figure: 1 PRISMA Flow Diagram for the Systematic Review

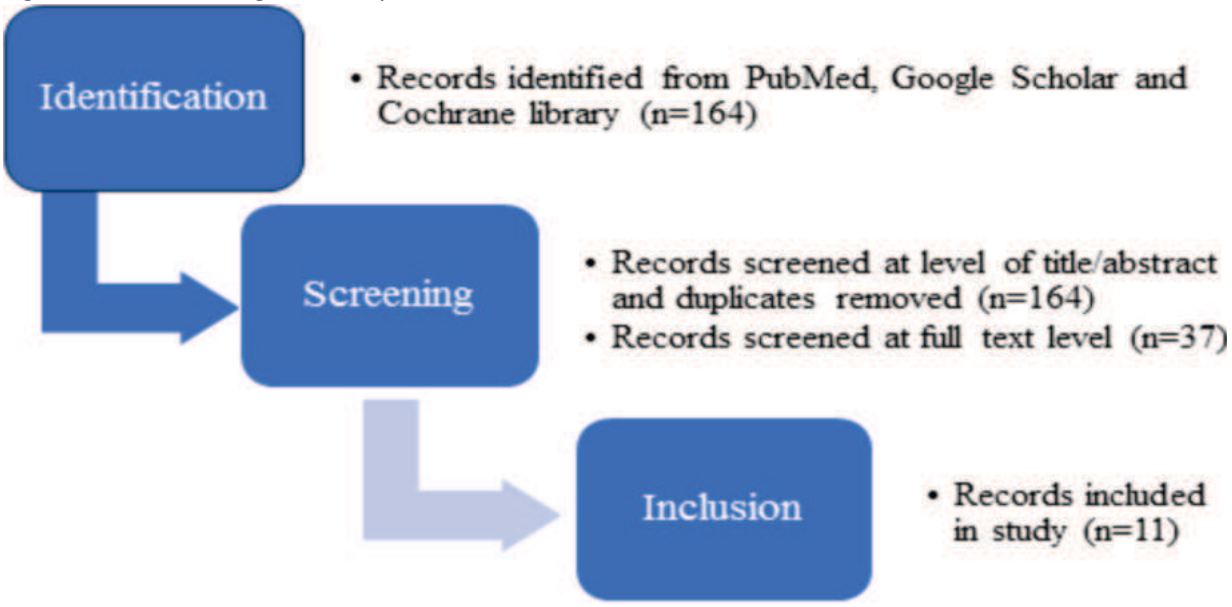

Table 2: Study Characteristics of the Included Studies

Sr. No.	Sample size (cases with family history)	Average Gestational age at diagnosis	Cases diagnosed correctly on USG	USG protocol	Diagnostic criteria	Other investigation	Outcome of pregnancy	Conclusion
1	3 (0)	N/A	3/3	N/A	N/A	amniocentesis	2-TOP 1-delivery at term	Genetic counselling is important in familial diseases
2	3(0)	31	3/3	N/A	Shortening and bowing of long bones, Fractures of femur and ribs	3D CT	2-CS(1-at term,1-preterm) 1-neonatal death	USG in conjunction with 3D CT provides better diagnostic sensitivity and specificity
3	2(0)	34	2/2	N/A	Shortening and bowing of long bones, bone fracture, decreased mineralization	3D HCT	1-TOP 1-CS at term	Same as study 2.
4	12(0)	22	12/12	N/A	Short long bones with bowed humeri and femurs	Amniocentesis and rapid medical trio exome Sequencing (ES)	8-TOP 4-delivery live birth	USG & medical trio ES can be reported in 2 weeks, with the timely report aiding in parental counselling and decision making
5	10(0)	25	10/10	N/A	Shortening and bowing of long bones, with a narrow thorax, protuberant abdomen, bone mineralization, multiple bone fractures, polyhydramnios	-	10-TOP	USG is helpful in prenatal diagnosis and can be combined with molecular studies
6	6(0)	21.6	5/6	2 or >2	N/A	No	5-TOP 1-death in neonatal period	All screening and dating obstetrical sonograms confirmed by experienced sonographer help in antenatal detection of lethal skeletal dysplasias
7	40 (19)	23	18/40 (all 8 cases of type 2 OI diagnosed prenatally)	N/A	N/A	N/A	13-live birth (5 died in neonatal period all type II) 4-TOP 1-stillbirth	Medical practitioners involved in maternal and prenatal care require a better understanding of outcomes and inheritance patterns of skeletal dysplasias for counselling and coordination
8	2(2)	14	2/2	Serial TVS examinations were performed every 2 weeks from 10–11 weeks; and detail scan at 20–22 weeks	Poor ossification of the calvarium, shortening of the long bones, demineralization of the skull	No	2-TOP	Early diagnosis in 1st trimester is difficult and the differential diagnosis makes it more complex. Measurements charts could be useful for early diagnosis in selected high-risk patients. USG at 18–22 weeks, therefore, remains mandatory.
9	7(N/A)	28	7/7	N/A	Lung volume measured with VOCAL method and considered abnormal when it was below a reference interval of 5% on the basis of the expected average for the gestational age	No	4-died 3-lived	3D US is an accurate and a non-invasive method for predicting lethal pulmonary hypoplasia in cases of skeletal dysplasia
10	15(4)	21.5	15/15	Second trimester but number of scans N/A	Short limbs, abnormal head, Oligohydramnios, Odd lower limbs, small chest	No	12- TOP 1-spontaneous abortion 1- Still birth 1- Neonatal death	Diagnosis of OI can be possible with USG, but differentiation between subtypes is difficult
11	6(0)	26	6/6	USG done due to various risk factors for OI	Bone shortening, diffuse hypomineralization and multiple fractures of long bones including beaded ribs	No	6- TOP	Classical sonographic features of OI type IIA include severe micromelia with deformity, diffuse hypomineralization and multiple fractures of long bones including beaded ribs.
	106(25)	24.6 (mean)	83			TOP- 50 Still birth/neonatal death/spontaneous abortion- 15 Livebirth-19 (3-CS)		

TOP- Termination of Pregnancy, NVD- Normal Vaginal Delivery, CS- Caesarean Section, USG- Ultrasonography, CT- Computed Tomography, VOCAL- Virtual organ computer-aided analysis
Article Serial Numbers are as per ROB analysis table.

3.2. Study Samples and USG Diagnostics Criteria

Total number of cases were 106, out of which 25 has positive family or past history. 83 cases were identified correctly by USG, while remaining cases were not identified or wrongly identified as some other skeletal dysplasia.

Mean gestational age of diagnosis was 24.6 weeks with range of 14 to 34 weeks. Most of studies included has identified positive cases in second trimester.

Most of studies has not specified number of USGs done for diagnosis and duration between each USG, thus proper protocol has not been mentioned. Only 2 studies (Tretter et al and Gabrielli et al) have described it as shown in table 2. Constantine et al done USGs in 2nd trimester but protocol not specified, while Tongsong et al done USGs in high-risk cases for OI.

Common diagnostic criteria employed in various studies for identification of OI, particularly of lethal OI type II include short limbs (shortening of long bones), diffuse hypomineralization, multiple long bone fractures including beaded ribs. Other features include chest hypoplasia, oligohydramnios, poor ossification of calvarium, bowing of long bones.

3.3. Additional Investigations Done in Included Studies

Most of studies has not employed any additional investigation for diagnosis, except some few. Most commonly employed additional investigation include amniocentesis and Han et al has done rapid medical trio exome Sequencing (ES) after amniocentesis, while Ruano et al and Waratani et al employed 3D CT.

3.4. Outcome of Pregnancy

Out of 106 total pregnancies included 83 were diagnosed in prenatal period and outcome of 84 pregnancy were mentioned. 50 out of 84 pregnancies were underwent termination of pregnancy. 15 pregnancies result in still birth or spontaneous abortion or death in neonatal period. 19 pregnancies result in live birth out of which 3 had caesarean section (CS), among which one was preterm.

3.5. Conclusion of Studies

Most of studies confirm that USG is a cheap, non-invasive and effective method of screening and diagnosis of OI, particularly of lethal type II and parental counselling in perinatal period regarding outcome of pregnancy, particularly in second trimester of gestational period. 3D US is better than 2D US. Some studies employed it in 1st trimester also, but it was not as accurate as in 2nd trimester and differentiation with other skeletal dysplasia makes it more difficult. Quality and skillset of sonographer is also important. While amniocentesis combined with molecular or genetic studies was more accurate but invasive nature, cost and resources in remote location limits its widespread use. 3D CT is also effective method in OI diagnosis but ethical considerations of radiation exposure to embryo and its effects limits its use.

4. DISCUSSION

OI is the name given to a variety of heterogeneous connective tissue conditions in which defective type-I procollagen formation occurs.[5] Type II is distinguished by a tiny thorax, various degrees of hypomineralization, extensive rhizomelia, and bone irregularity and bowing from repeated fractures. These kinds of fetal ultrasound findings include numerous fractures, severe shortening and bowing of the long bones, narrow thorax associated with multiple rib fractures and a compressible, thin calvaria that appears translucent on sonography.[18]

The prevalence of skeletal dysplasia varies from 2.3 to 7.6 per 10 000 births and is 1.5 per 10 000 births for lethal skeletal dysplasias. Despite their rarity, these anomalies are relevant for the sonologist, as they are often familial and require prenatal diagnosis.[16]

Obstetric ultrasound has become a standard component of antenatal care.[19] Prenatal diagnosis of skeletal anomalies, even extremely early in pregnancy, has been reported in the literature, but it is clear that this is only following targeted examination by experienced sonographers on the basis of dysmorphological ultrasound findings.[20,21] In addition, chorionic villus sampling and DNA analysis may also have assisted early prenatal diagnosis.[21] Second trimester anatomic scan is still the standard investigation for the detection of fetal structural anomalies and growth.[22]

Many pregnant women, receiving a prenatal detection of fetal anomalies is frequently associated with intense feelings of shock and grief; the extent of which is related to the gestation age and the condition diagnosed and is aggravated by the uncertainty of the diagnosis. In such cases, well-defined standards for the diagnosis of osteogenesis imperfecta are useful. After knowing the diagnosis with possible poor prognosis many parents may choose to terminate the pregnancy and those who elect to carry the pregnancy to its conclusion may also benefit by allowing them to forgo obstetric interventions, such as caesarean section for fetal distress.[17,22]

Biometric charts of first-trimester fetal limb segment measurements have recently been available.[23,24,25,26] However, the potential of these measurements to increase the accuracy of an early diagnosis has not yet been established and in most skeletal dysplasias, limb growth impairment becomes apparent only late in pregnancy.[27]

Most Commonly Employed Diagnostic Criteria are:

1. The femora measured more than 3 standard deviations (SD) below the mean femoral length for gestational age.[17]
2. Demineralization of fetal bones, as judged subjectively according to the appearance of the calvaria. This is based on two separate observations: marked diminution or virtual absence of the usually seen brightly echogenic calvaria margin and marked enhancement of brain visualization.
3. Presence of multiple fractures, as demonstrated by more than one discontinuity along the length of a single long bone and by a wrinkled appearance of the cortex of the bone.[17]

Other methods of prenatal diagnosis are 3D CT, amniocentesis and karyotyping, exome sequencing (ES) and Chromosomal Microarray, but all have their limitations.

3D CT has possible risk of radiation exposure to fetus, although authors concluded that 3D-HCT identified more postnatal skeletal findings than 3D-US. This is due to 3D-HCT provided images can be stored and analysed further by a radiologist and a geneticist, while the 3DUS provided images were analysed only by the physician sonographer.[28] Fetal exposure to radioactivity is very similar to that of conventional fetal radiological examination (3 mGy) and to that provided by pelvic CT scanning in pregnancy (3 mGy). Advantages of 3DUS include fewer movement artifacts, no radiation exposure and cheap and wider reach in healthcare facilities in remote areas.[28,29]

Genetic testing is recommended when a fetal structural abnormality is detected, to determine nature of it. Chromosomal microarray is preferred as a first-line test. Exome sequencing (ES) technique's use is growing in recent years.[2,3,6] They have disadvantages of being invasive in nature, expensive and only available at tertiary centres limiting its utilization. Another problem is that most cases of OI is due to spontaneous mutation rather than familial.

Limitations of USG includes availability of skilled sonographer, more subjective in nature. Additionally, measurement of these parameters at such early stages requires experience, to obtain the best scan to visualize the entire bone segment, which measures just a few millimetres. This could explain why diagnosis in 1st trimester is difficult. Thus, an ultrasound examination at 18–22 weeks is mandatory. [2,16] Any fetus showing shortening of long bones should be evaluated further for confirmation of diagnosis at centre with expertise.[2]

At present, a definitive diagnosis of fetal OI is initially based on morphological, radiological features. Advances in molecular genetics have helped elucidate the biological basis and the genotype–phenotype correlations of OI, making this technique amenable to invasive prenatal diagnoses.[2,16]

5. CONCLUSION

Cultured chorionic villi cells, molecular biology and genetic studies offer new possibilities of prenatal diagnosis of OI, but USG remains the investigation of choice. In positive past history, ultrasound starting as early as 11 weeks of gestation or chorionic villus sampling should be

discussed. For all pregnancy detail 2nd trimester scan should be performed at around 20 weeks of gestation for early diagnosis by expert sonographer. We conclude that the triad of Shortening and bowing of long bones, multiple bone fracture including beaded ribs, decreased bone mineralization on prenatal sonograms permits a confident diagnosis of OI. Additional features include chest hypoplasia, oligohydramnios and poor mineralization of calvaria. Accurate diagnosis has huge ethical implications on genetic counselling and decision making of parents especially in lethal type II.

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