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Assessment of Fetal Skeletal Abnormality by Ultrasonography

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ABSTRACT

Reported rates of sonographic detection of fetal anomaly vary widely. The purpose of this study was to determine the ability of the Fetal Medicine Unit at the University College Hospital London, in detecting fetal skeletal anomaly and to compare the results with other published series. The sonographic studies done in 208 skeletal abnormalities over 6 years period with pregnancy outcomes established by medical records and pathologic results of the infants whether born alive or dead were compared. Of these 65 (31%) cases were chromosomally abnormal, 20 (9%) cases had neural tube defects (NTD), 15 (7%) cases were multiple fetal abnormalities, 6 (3%) cases were intrauterine growth retardation, 35 (17%) cases had positional deformities, 8 (4%) cases were with formation of individual bones, 2 (1%) cases with non-syndromic digital abnormalities and 30 (14%) cases had skeletal dysplasias. In 17 (8%) cases no diagnosis was established whether based on gross morphology or pathological reports. The postnatal examinations confirmed the prenatal sonographic prediction in 122 (58.7%) cases. The prediction rate varies from 90% for cases of NTD to 36% for cases of skeletal dysplasias. These results compare favorably with those reported in other series.

Disturbance of the normal process of bone growth and modeling results in a heterogenous group of skeletal abnormalities. Prior to the introduction of sonography, the prenatal detection of skeletal disorders in utero was possible only by using radiographs obtained during pregnancy. This was achieved by performing either a flat x-ray of the maternal abdomen or amniography. Currently, the diagnosis of many skeletal disorders is feasible due to improved ultrasound resolution, better sonographic skill and experience, and a more precise understanding of fetal embryology and development. With the increased utilization of ultrasound screening programmes, the rising trend in detection of skeletal malformation will continue.[1]

Incidence of skeletal abnormality

Using s population-based register of congenital anomalies, 2 demonstrates a prevalence rate of skeletal malformation of 3.22 per 10,000 live births. However, this figure may not be a true representation of all skeletal anomalies because of its coexistence with various other syndromes. In addition many pregnancies terminate before reaching the registering stage.

Neural tube defects occur 1 in 1,000 births and

many cases are prevented by providing mothers with folic acid prior to conception. Up to 5% of neural tube defects occur as part of the autosomal recessive Meckel syndrome which is a multiple malformation syndrome associated with neural tube defects, hydrocephalus and polydactyly, as well as a variety of other defects.[3] Twenty-five percent of all conceptus have a major chromosomal defect and 6% of all malformed infants are due to a chromosomal abnormality.[4]

Intrauterine growth retardation complicates 5% of pregnancies due to placental insufficiency. However defective bone growth is not always an adverse effect of these conditions. Isolated talipes occurs in about 1 in 1,200 pregnancies but it may be an integral part of a genetic syndrome.[5] Not infrequently (1 in 2,000 births) abnormal fusion of the fingers or toes (syndactyly) occurs and in some cases this leads to fusion of the bones.[6] A multi-hospital birth defects register, the Latin American Collaborative Study of congenital malformation (ECLAMC), reported the birth prevalence of skeletal dysplasia as 2.3/10,000 births.[7]

Table 1. Classification of skeletal abnormalities

Class	Type
A	Neural tube defects associated skeletal abnormalities
B	Multiple fetal abnormalities including skeletal anomalies with normal karyotype
C	Skeletal disorders associated with abnormal karyotype
D	Defects in bone growth
E	Positional abnormalities
F	Malformation of individual bones
G	Digital abnormalities
H	Skeletal dysplasias
I	Unidentified

Aetiology

There are known molecular basis for various skeletal malformations, 8 however not all development defects are necessarily genetic in origin and various aetiological categories can be recognized.

1. Chromosomal anomalies (e.g. trisomies, translocations)
2. Polygenic disorders (e.g. short stature)
3. Single gene mutation (e.g. achondroplasia, cleft palate)
4. Environmental/teratogenic factors (e.g. phenytoin, warfarin)
5. Multifactorial aetiology (e.g. neural tube defects)
6. Unknown aetiology

The phenotype is determined by the product of the combined effects of genetic and environmental influence, 9 but the relative contributions of each can differ for each aspect of the phenotype. Limb defects associated with other abnormalities are often heritable. As the most important events in limb development occur between the fourth and eight week post-fertilisation, this is also the period of higher susceptibility to teratogens or defective expression of developmentally regulated genes.[10] However, limb defects can also occur as a consequence of trauma once development of all the limb structures has been accomplished. For example, secondary disruption, so called intrauterine amputation, is thought to be caused by constriction of the developing limb due to exogenous pressure or disturbance of blood supply.[11]

Diagnosis of skeletal abnormalities by real-time ultrasound

Routine ultrasonography in a low-risk population

of pregnant women has led to increased identification of fetuses affected with a skeletal abnormality in the second trimester.[12] However, establishing a specific diagnosis in utero is often difficult since sonographic findings are not necessarily pathognomonic of a postnatal diagnosis.[13]

First trimester ultrasound scan has limited usefulness in the early detection of skeletal abnormalities apart from the diagnosis of neural tube defects and early dating of the pregnancy. Hewitt (1993)[14] reported a case of skeletal dysplasia in the second trimester who had increased thickness of nuchal fold in the first trimester and normal karyotype. In a larger series of first trimester scan[15] suggested the possibility of increase findings of skeletal anomalies in eukaryotype fetuses with increased nuchal translucency.

Most skeletal abnormalities are diagnosed between 18 and 20 weeks, when most women attended for a fetal anomaly scan.[16] The other cluster of cases is found in the third trimester as a result of ultrasound diagnosis performed for the investigation of polyhydramnios, intrauterine growth retardation, premature labour, or intrauterine fetal death.

Most routine screening examinations have included measurements of the head, abdomen and femora.[17] At this time the ultrasonographer may detect a skeletal abnormality. The long bones may be abnormal not only in size but also in shape. An abnormal screening ultrasound should result in a more intensive study (e.g. if the femoral measurements are abnormal) progressive to a detailed examination that includes all the long bones: humerus, radii and ulnae as well as the tibiae and fibulae.[18] A special linear chart is prepared for the future sonographic assessment and growth.[19] An attempt should be made to assess the degree of mineralisation by examining the acoustic shadowing behind the bone; the echogenicity of the bone itself and the possibility of fractures should be considered.

A small or constricted thorax often leads to neonatal death because of respiratory difficulties. Thoracic dimensions can be assessed by measuring the thoracic circumference at the level of the four chamber view of the heart.[20] Special note should be made of the shape and integrity of the thorax.[21]

A sagittal view of the head permits the determination of midface hypoplasia[22] which occurs in several bone disorders.

Finally the skull shape, mineralisation and degree of ossification should be evaluated to obtain as much information as possible for a specific dianosis.[17] In addition, non-skeletal abnormalities such as cardiac defects and kidney malformation may be helpful clues to the diagnosis of a specific skeletal dysplasia. Besides a specific diagnosis, which is often very difficult, a probable lethal condition can often be detected with this detailed examination.

Current management of prenatally diagnosed skeletal abnormality

The initial management following the diagnosis of a suspected skeletal abnormality is to arrange for a detailed fetal scan to look carefully for other abnormalities which may influence the prognosis and future follow up. Karyotyping should be discussed with potential parents as various chromosome disorders have skeletal abnormalities as discussed earlier. This is carried out using cytogenetic culture and sometimes the more urgent FISH (Fluorescence in situ hybridisation) technique for the detection of Trisomy 13, 18, 21 and sex chromosomes.[23] Establishment of fetal sex is important in the diagnosis of Camptomelic dysplasia.

Close examination of both parents for signs of skeletal disorder is of value in the rare possibility of autosomal dominant inheritance. Some families may be faced with the 25% recurrence risk associated with autosomal recessive inheritance. It is usually impossible to designate these families, although consanquinity or a previously affected child may be suggestive.[24]

The important of serial examinations by ultrasound scan should be borne in mind and the use of alogarithms and growth charts are utilised for assessing fetal development.[19] A second look

assessment is carried out for solitary and minor abnormalities like clubfoot which are managed expectedly.

Counseling

The increasing use of routine ultrasound in recent years has allowed for prenatal of optimal care for fetal malformation.[25] In addition there has been a greater understanding of the natural history of skeletal abnormalities in recent years due to advances in ultrasound imaging. Some parents will take the decision to interrupt the pregnancy whilst others will opt to continue in the hope of a more favourable perinatal outcome. Identification of prenatal factors that are useful in counseling will help parents make these difficult decisions. In all cases the parents should be offered the opportunity to discuss the diagnosis, prognosis and subsequent management with a paediatrician, orthopaedic surgeon and/or a geneticist.

Diagnosis and risk assessment

Without an exact diagnosis precise risk assessment is not possible. A diagnosis adequate for management is not always sufficient for genetic counseling. This emphasizes on the need for the geneticist to be involved in the diagnostic process especially where oppourtunities for further examination may not exist. This occurs, for example, after termination of a fetus as a result of prenatal diagnosis or in the case of very sick newborn infants.[26]

Termination of pregnancy (TOP)

At present, terminations performed on pregnancies up to fourteen weeks gestation is by uterine aspiration as a one stage procedure. Between fifteen weeks and twenty three weeks local application of prostaglandin is the more preferable mode of termination.[27] Live fetuses of more than twenty three weeks require fetocide to prevent a live birth. Cardiac asystole with the injection of potassium chloride into the heart prior the induction of labour is performed. Patients should be informed of this procedure if they are considering late termination of pregnancy.

Postmortem examination

The purpose of fetal examination of following termination of pregnancy after detection of fetal anomaly is vital for postnatal parental counseling for recurrence risk. It is also important to establish our accuracy or prenatal diagnosis.[28] This procedure should be explained to the parents to permit calculation of recurrence risks of the disorder for that particular family. Basic fetal examination comprise naked-eye examination including careful measurement and recording of anomalies, radiographic examination followed by visceral dissection and histological examination of major organs.[29] A photographic record of all external dysmorphic features as well as any visceral anomalies provides a permanent record of the abnormalities, particularly important for a future consultation in usual cases. Tissue culture, chromosome analysis, DNA analysis may be necessary depending on the type of the anomaly found. Macerated fetuses create difficulty in reaching a diagnosis particularly in assessing the central nervous system (CNS) abnormality. Postmortem axial skeletal radiography can reveal fetal CNS malformation otherwise missed in routine autopsy.[30]

The study

The study was retrospective, it took place in the Fetal Medicine Unit at University College Hospital London which is a tertiary referral center for fetal diagnosis in North East Thames and surrounding regions. The aims were to determine the accuracy of our prenatal diagnosis of skeletal abnormality, the uptake of postmortem and karyotyping and the incidence of cases of skeletal abnormality to the Fetal Medicine Unit.

Method

The cases suspected of skeletal abnormalities are assessed by one five fetal medicine specialists staffing the unit. A detailed ultrasound scan is conducted and the data stored on the software programme. Following this detailed assessment the

clinical information regarding the possible diagnosis are discussed with the patient. Further tests including fetal karyotype are carried out in the initial visit or subsequent visits.

The information was obtained from the database search between January 1993 and December 1998. A questionnaire was sent for data collection from General Practitioners and Hospitals. The information includes postmortem reports, x-rays and in the case of continuing pregnancy any paediatric reports and follow-up management.

The information was complied in a work sheet which contains the case number, ultrasound findings, outcome (e.g. termination of pregnancy or live birth etc.), postnatal diagnosis and prenatal predictions.

Results

Between January 1993 and December 1998; 4,800 new cases of fetal anomalies were seen in the Fetal Medicine Unit. During this time, there were 254 cases of suspected fetal skeletal abnormality. This constitutes a referral rate of 5.3% incidence in our referral population of suspected fetal skeletal anomaly.

Full analysis of 208 (80%) cases was possible where outcome, karyotype findings, postnatal assessment or postmortem examination were available for review.

Complete information was not obtained in 46 cases as questionnaires were not complete by the time the study finished (n=30), patients were not traceable (n=3), postmortem was not performed (n=1), or the parents refused postmortem examination (n=12).

Fetal karyotpe

Invasive procedures for fetal karyotpe was performed in a 136/208 (53.5%) cases. An abnormal karyotype was found prenatally in 63/136 (46%). Two cases were offered karyotyping in the prenatal period on the presumed diagnosis of aneuploidy but this was declined. Both cases were confirmed trisomy 13 and trisomy 18 postnatally.

There were 208 cases in the study. Appendix I and Appendix II summarises these cases (n= 143) excluding all those with abnormal karyotype (n=65) pre or postnatally determined. In the table is listed the ultrasound findings, outcome, prenatal diagnosis and postnatal diagnosis.

The postnatal diagnosis of the study group is shown in Fig. 1, according to the classification. In addition there are 10 anomalies suspected on prenatal sonograms that were not confirmed clinically in the immediate postnatal period. Nine of these cases were live births, and one had a postmortem examination after a terminated pregnancy.

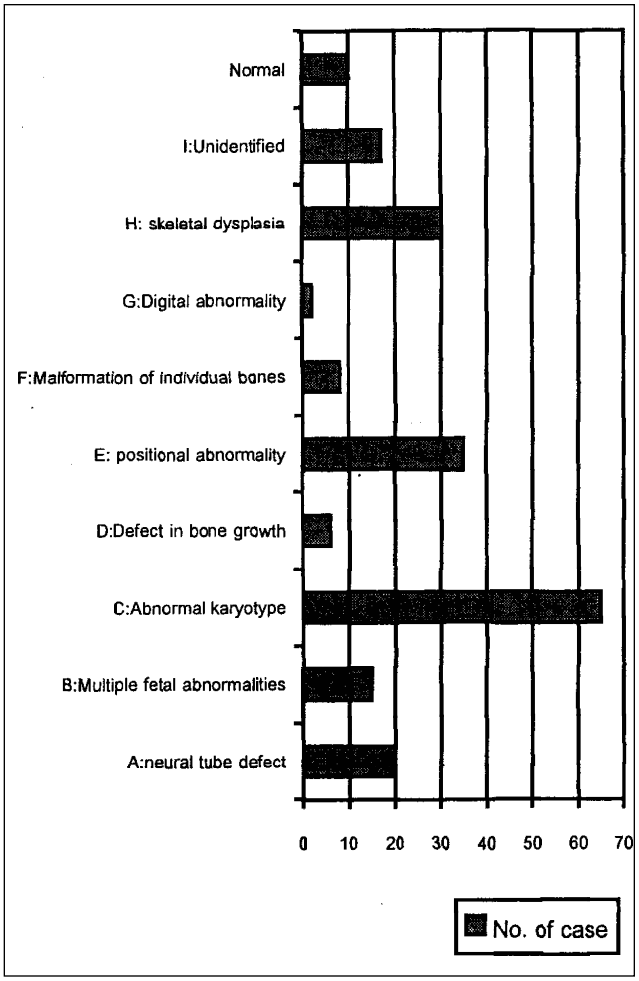

Fig. 1. Postnatal diagnosis of cases suspected of prenatal skeletal abnormalities (n=208).

Group A Neural tube defects : NTD's were confirmed in 19 cases prenatally, and 1 was later diagnosed by postmortem. Four of the cases (20%) were found to be Meckel syndrome, at the postnatal follow-up/ or postmortem. This is higher than the expected association rate of 5% in previously reported incidence of Meckel syndrome in the prenatally diagnosed NTD's.[3]

Group B Multiple fetal abnormalities : Fifteen cases of skeletal anomaly were associated with a variety of other fetal abnormalities prenatally. These were grouped together and classified as multiple fetal abnormalities or non-syndromic dysmorphic fetuses postnatally.

Group C Abnormal karyotype : Abnormal karyotype was found prenatally in 63 cases. Another 2 cases were confirmed in the postmortem examination. This group did include a variety of skeletal anomalies e.g. short femur, radial aplasia, polydactyly which were not evaluated in details in this study.

Group D Defects in bone growth: Intrauterine growth retardation and short stature was diagnosed in 5 cases in the first month of postnatal life. Another case was terminated because of the predicted adverse outcome, proved to be a parvovirus infection. Only 1 of these cases was rightly predicted in the prenatal period.

Group E Positional abnormality: Prenatal sonographic assessment was carried out on 35 cases of suspected talipes. Fourteen (40%) cases were karyotyped. Twenty two cases were confirmed isolated talipes, and six were associated with other anomalies described in Table 2. Seven cases of the isolated talipes were normal in the postnatal period.

Table 2. Talipes associated anomalie

Associated anomaly	No. of cases
Cleft lip, cleft palate	1
Gastroschisis	1
Kippel-Trenaunay Weber	1
Hydronephrosis	1
Sacral agenesis	1
Major limb deformity	1

Group F Malformation of individual bones: The formation of individual bones (n=8) are divided in Table 3. Two patients electively terminated the pregnancy. The prenatal prediction was confirmed in all cases.

Table 3. Malformation of individual bones

Abnormality	No. of cases
Limb reduction defects	4
Isolated short femur	3
Short radious and ulna	1

Group G Digital abnormality: There were 2 cases of hand deformity; one, with non-syndromic polydactyly and the second, was autosomal dominant ectrodactyly. The latter cases had a family history of Le Main Fendue syndrome. Both cases were correctly predicted prenatally.

Group H Skeletal dysplasia: Thirty cases of fetal skeletal dysplasia were diagnosed postnatally (Table 4). Prenatal diagnosis was achieved in 11 of these cases.

Table 4. Skeletal dysplasia cases diagnosed postnatally

Skeletal dysplasia	No. of cases
Osteogenesis imperfecta	5
Pena shokeir	3
Achondroplasia	3
Hypochondroplasia	1
Short rib polydactyly	1
Smith-Lemi-Opitz	2
Chondrodysplasia punctata	1
Thanatophoric dysplasia	4
Yunis-varon syndrome	1
Larsen's syndrome	1
Cornelia de lange	1
Achondrogenesis	1
Holt Oram	1
Thrombocytopenia-absent radius	1
Bloomstrand chondrodysplasia	1
Arthrogryposis	3

Group I Unidenfined: Twenty nine cases had unidentified diagnosis postnatally, 12/29 (41%) cases because parents declined postmortem examination. The remaining 17 cases were 5 live births, 9 terminations, 1 intra-uterine death, and 2 neonatal deaths. All five live births had short long bones with or without other association anomalies. They did not fall into one of the eight distinct classifications mentioned above.

The final postnatal diagnosis confirmed the prenatal prediction in 122 cases. This is 122/208 (58.7%) accuracy of prenatal diagnosis of all cases of skeletal abnormality. Ten cases with prenatally diagnosed skeletal abnormality were found to be normal in the immediate postnatal period.

Uptake of postmortem

There were 66 autopsy examinations performed on 5 NND, 8 IUD and 43 TOPs. The total number of terminations were 130/208 (63%) cases. Twelve parents refused to consent for postmortem; an uptake of 84%. These cases have been taken out of the final analysis. Reports of the postmortem were in-conclusive in 13/66 (20%) cases. In 31 (47%) cases, the prenatal diagnosis was confirmed by autopsy. In only two cases (3%) the prenatal diagnosis was confirmed by autopsy. In only 2 cases (3%) the prenatally detected malformation was not confirmed by pathological examination.

Discussion

Prenatal detection of skeletal abnormalities has become increasingly common; however, reaching a final diagnosis is still not easily achieved prenatally. The most likely time of diagnosis is between 18 and 20 weeks, which is around the time of the first routine ultrasonographic examination. Familial cases tend to be diagnosed earlier in gestation because of the more careful and early assessment. Evaluation of a fetus at risk of abnormal development of the skeletal system requires careful scanning of (1) upper and lower extremities, (2) cranium, (3) thorax and (4) abdomen. The prenatal management of a suspected diagnosis of fetal abnormality is based on the likely prognosis. Termination of the pregnancy should be a decision of the parents after they have received appropriate

genetic and perinatal counseling.

Many of the cases referred to the Fetal Medicine Unit were without a specific diagnosis. In this study the prenatal diagnosis was accurately achieved in 58.7% of cases. There are 10/208 (4.8%) cases which had suspected skeletal abnormality on prenatal ultrasound but were shown to be apparently normal postnatally. It might create some concern to the accuracy of the prenatal diagnosis especially with regard to the limited information that can be obtained from ultrasound. The majority of these cases, were to do with femur length measurements and some of the normal fetuses were judged to have short limbs probably because of its constitutional nature or the association with certain ethnicity. Under-estimation of the fetal long bones is also possible if a tangentional cut of the bone has been scanned due to the fetal position. All the prenatally diagnosed, false positive cases for suspected skeletal anomaly above ended in a live birth except one which was a twin gestation that was terminated on the assumed diagnosis of neural tube defect. The postmortem findings were normal.

Of the cases referred to the Fetal Medicine Unit with suspected skeletal anomaly 136/208 (65%) proceeded to invasive testing. Abnormal karyotype was found in 65/208 (31%) of these cases. It is shown that almost half of the amniocentesis carried out for predicted chromosomal aberrations were abnormal. As we develop more knowledge of these disorders the number of unnecessary invasive procedures becomes less and priority in the management will be focused on the assessment of prognosis. This is brought about by the improvement in diagnosis.

Out of the 20 cases of neural tube defect, 18 (90%) were accurately diagnosed in the prenatal period. These results are similar to various other studies of prenatal sonography.[31] It is probably due to acquaintance of the sonographer with these conditions as they easier to recognize on routine scan (Brain signs) and secondly, mid-trimester serum screening for raised alpha fetoprotein is a useful adjunct to scan. One case that missed the right diagnosis was originally referred because of spina bifida but was incorrectly labeled as vertebral anal tracheo-esophageal renal (VATER) association in the prenatal period and the postmortem confirmed a neural tube defect. The second case was diagnosed as isolated talipes and was later found to be associated with sacral agenesis.

In all cases of talipes (n=35) there were 7 (20%) cases which had normal position of the feet in the postnatal period. In addition, there were 2 cases; one where talipes was diagnosed postnatally in association with more severe limb deformities and the other with sacral agenesis. This is probably because cases of isolated talipes were not considered as conditions with adverse postnatal outcome and hence they had only one second look follow up with ultrasound scan before due date. Nevertheless, they did receive close attention particularly in searching for other markers of aneuploidy or in the case of elder mothers an amniocentesis was carried out for karyotyping in 14 (40%) of cases.

There were few cases of non-syndromic abnormal digits (2 cases). Whether this is the true representation of this disorder is not really known. The hand can be assessed more critically than the foot but is frequently clenched in fist-like fashion, which can complicate the counting of fingers. However, even under these circumstances one can frequently make the necessary observations. It requires time, patience and skill.

The prenatal ultrasound scan is very useful in the diagnosis of limb reduction deformities. Although only 8 cases were scanned with such abnormalities, isolated limb defects were distinquished from the more serious disorders such as TAR (Thrombocytopenic-absent radius), Holt-Oram or Robert's syndrome. Prenatal sonographic examination correctly predicted the diagnosis in 11 (36%) of the 30 cases with skeletal dysplasia. This is slightly higher than the published report on prenatal sonographic diagnosis of skeletal dysplasias by Gafney et al, (1998) [32] at Oxford Radcliffe Hospital where they achieved an accurate diagnosis in 31% of 35 cases. There was one case which was prenatally judged as skeletal dysplasia but was later diagnosed as an intrauterine growth

retardation. The likely prognosis in cases of suspected skeletal dysplasia is important and usually based on the severity of the skeletal abnormality like limb shortening, angulation, chest size, and associated sonographically identified abnormalities (e.g. hydrops). In 22 (73%) of the 30 cases in this study, the sonographic assessment suggeste the condition present was probably lethal. The ability to predict this outcome prenatally would be important in counseling parents. A reduced femur length-to-abdominal circumference ratio is used in some studies as a predictive value for lethal skeletal dysplasias.[33] This is not a routine practise at University College of London (UCL), Fetal Medicine Unit. It is a measurement not without its reservations especially in fetuses with moderate instead of severe shortening of the femurs that may have lethal abnormalities, and yet do not fall below the cut off limit for predicted lethality.

Terminations of pregnancy for all prenatally diagnosed skeletal abnormality were 130/208 (63%) cases. 22 were prenatally diagnosed skeletal dysplasias. Other abnormalities include those who had predictive poor prognosis from prognosis from the physical or mental point of view. Only 2 couples opted to terminate the pregnancy where minor to moderate physical disability was predicted (isolated absent radius and forearm limb reduction).

Diagnosis of fetal anomalies with ultrasound has improved since the first reported termination of pregnancy after ultrasound prenatal diagnosis.[34] This is due to the improvement in machine resolution and the specialists skills and expertise. However, there is still s big gap that is needed to bridge before approaching the time when prenatal diagnosis is easily reached in at least 80% of cases. Newer technologies like molecular biology or 3D scan may alter the prediction rate in the prenatal diagnosis of skeletal abnormality in the future. Care in the meantime should be exercised until more fetuses have been studied and followed to delivery.

In conclusion, in this study the Fetal Medicine Unit at University College Hospital London has successfully diagnosed prenatally 58.7% of cases referred with suspected skeletal anomaly, confirmed postnatally. The false positive rate was 4.8%. The fetal karyotype was abnormal in 30% of these cases. The uptake of postmortem following neonatal death, intrauterine fetal death and termination of pregnancies was 84%. In order to improve understanding and management of the prenatally diagnosed suspected skeletal abnormalities, outcome data is vital. The postmortem for terminated cases plays a vital role in achieving this. The Fetal Medicine Unit Specialist is the crucial person to introduce this concept when managing a complicated case that opts for a termination of pregnancy.

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