

# Correlation between ultrasound diagnosis and autopsy findings of fetal malformations

Antonella Vimercati  
 Silvana Grasso  
 Marinella Abruzzese  
 Annarosa Chincoli  
 Alessandra de Gennaro  
 Angela Miccolis  
 Gabriella Serio  
 Luigi Selvaggi  
 Fabiana Divina Fascilla

Department of Obstetric and Gynecology, University of Bari, Italy

## Corresponding author:

Annarosa Chincoli  
 Department of Obstetric and Gynecology  
 University of Bari  
 Piazza Giulio Cesare, 11  
 70124 Bari, Italy  
 Mobile: +39 3934272995  
 E-mail: annarosa.chincoli@virgilio.it

## Summary

**Objective:** to compare ultrasound (US) and autopsy findings of fetal malformations in second trimester terminations of pregnancy to evaluate the degree of agreement between US and fetal autopsy.

**Methods:** in this study, all second trimester termination of pregnancy between 2003-2010 were considered.

**US and autopsy findings were compared and all cases were classified into five categories according to the degree of agreement between US and pathology (A1: full agreement between US and autopsy; A2: autopsy confirmed all US findings but revealed additional anomalies 'rarely detectable' prenatally; B: autopsy demonstrated all US findings but revealed additional anomalies 'detectable' prenatally; C: US findings were only partially demonstrated at fetal autopsy; D: total disagreement between US and autopsy).**

**Results:** 144 cases were selected. In 49% of cases there was total agreement between US and autopsy diagnosis (A1). In 22% of cases additional information were about anomalies 'not detectable' by US (A2). In 12% of cases autopsy provided additional information about anomalies not observed but 'detectable' by US (B). In 13% of cases some anomalies revealed at US, such as valve insufficiencies, pericardial and pleural effusions, were not verified at autopsy (C). Total lack of agreement was noted only in 4% of cases (D). Main areas of disagreement concerned cardiovascular, CNS and complex malformations. The degree of

agreement was higher if malformations were diagnosed in a tertiary center.

**Conclusions:** this study shows an overall high degree of agreement between definitive US and autopsy findings in second trimester termination of pregnancy for fetal malformations. Autopsy reveals to be the best tool to diagnose malformations and often showed other abnormalities of clinical importance not detected by US, but sometimes also US could provide additional information about functional anomalies because US is a dynamic examination.

*Key words:* fetal malformations, fetal autopsy, prenatal diagnosis, prenatal ultrasound.

## Introduction

In industrialized countries, malformations are the first cause of prenatal death (25-30%) and are related to an elevated morbidity in the neonatal and post-natal period (1).

According to current laws about the theme of abortion, detection of fetal malformations at US is often the base for a subsequent voluntary termination of pregnancy. Considering the complex medical, ethical and social issues associated to this decision, the quality of US prenatal diagnosis and its detection rate should be carefully evaluated (2). Today with revolutionary technological improvements the resolution of ultrasound imaging has greatly increased. Together with the experience of operator, the possibility of "seeing the fetus" is presently emphasized and it is possible especially with second trimester (19-22 weeks) ultrasound, which has the aim to evidence structural abnormalities (2). Moreover, the use of high frequency transvaginal scanning sometimes has anticipated ultrasound screening, performed at 11 - 14 gestational weeks (3).

A number of studies (4, 2, 5-10) have tried to value the diagnostic accuracy of US examination, with very different results. The 'sensitivity' (i.e., the effectiveness of US in detecting the anomalies) of US varies between 14% and 85%, whereas the specificity (i.e., the ability of US in correctly diagnosing each malformation) ranges from 93% to 99%. These differences probably reflect the methodological problems of these studies. Moreover, prenatal US is a technique depending on the skill of examiners (2, 11), the kind of machines used for the examination and the organ system considered (2, 10).

Despite the US has reached a very high diagnostic accuracy, it has always some limitations and needs further studies. In fact fetal autopsy is obviously regarded as the 'gold standard' for assessing the effectiveness of US (2). The aim of this study was to evaluate the quality of prenatal US examination related to pathology findings and

the difference of diagnostic accuracy between first US and definitive diagnosis performed in a tertiary center.

## Materials and methods

The study covers the period from January 2003 to December 2010 inclusive. All terminations of pregnancy in the second trimester carried out at the Department of Obstetrics and Gynaecology in the Medical University of Bari, Italy, were reviewed.

The criteria for inclusion in the study were:

- 1) termination of pregnancy in the second trimester, carried out because of a prenatally diagnosed fetal malformation;
- 2) availability of data about both first and definitive US diagnosis;
- 3) possibility of performing autopsy;
- 4) availability of autopsy record.

Patients come to our center with a diagnosis of fetal malformation: the anomaly was diagnosed in another center and then evaluated again in our Department, that is a tertiary center, by a team of experienced ultrasonographers.

Gestational week was calculated from the last menstrual date; when the last menstrual date was uncertain, gestational week was calculated from the first trimester crown-rump length (CRL) measurement.

When a congenital defect was diagnosed, the couple was carefully counseled by the obstetrician in regard of prognosis, prenatal and especially postnatal care and the possibility of termination of pregnancy. In all cases colleagues from other fields such as neonatology, pediatric cardiology, pediatric surgery and neurosurgery were consulted, in order to evaluate all solutions to the problem. In our center, when a second trimester termination of pregnancy is carried out, autopsy of aborted fetus is always required. The autopsy reports were sent us from the Department of Pathology, Medical University of Bari.

The US reports were always available to the pathologists before autopsy examination.

All the data about termination of pregnancy, maternal age, gestational week at the time of US diagnosis and termination of pregnancy and karyotype (if known) were collected from the patient records. We considered both the first diagnosis and the one defined in our tertiary center. In five cases of CNS isolated malformations we performed fetal MRI.

All cases were classified according to the organ system (central nervous system - CNS, cardiovascular, thoracic, skeletal, gastrointestinal, genitourinary, head and neck, multiple anomalies, chromosomal abnormalities and other). Finally, all cases were divided into five categories to study the correlation between US and autopsy findings:

- category A1: full agreement between US and autopsy;
- category A2: autopsy confirmed all US findings but provided additional information about anomalies considered 'rarely detectable' prenatally;
- category B: autopsy demonstrated all US findings but provided additional information about anomalies judged 'detectable' prenatally;
- category C: US findings were only partially demon-

strated at fetal autopsy (some anomalies revealed at US were not verified at autopsy);

- category D: total disagreement between US and autopsy findings. In other words, the malformation whose prenatal diagnosis led to termination of pregnancy was not demonstrated at autopsy.

The difference between first and definitive diagnosis in the five classes was analyzed using the Fisher's exact test with GraphPad InStat. Differences were considered to be statistically significant at  $p < 0.05$ .

## Results

Of the 212 cases of termination of pregnancy initially considered, we effectively analyzed 144 cases with all complete data available, in order to evaluate the correlation between US and autopsy findings of fetal malformations whose prenatal diagnosis led to termination of pregnancy. At the time of the first diagnosis, mean gestational week was 18.9 (12-23) weeks; at the time of abortion it was meanly 20.3 (12-24) weeks. Only in 13 (9%) cases the US diagnosis was made before 14 gestational weeks.

Mean maternal age was 31.7 (range 19-46) years. Karyotype was known in 65 (45.5%) cases, and it was abnormal in 42% of the total: 3 cases of trisomy 21, 6 cases of trisomy 13, 7 cases of trisomy 18, 4 cases of Turner Syndrome and 7 cases of other chromosomal abnormalities (chromosomal deletions, trisomy 9, chromosomal insertions).

After division of malformations according to the organ system there were 23 (16%) CNS, 28 (19%) cardiovascular, 7 (5%) thoracic, 19 (13%) skeletal, 3 (2%) gastrointestinal, 9 (7%) abnormalities, which include cases of hygroma, hydrops, sacroccocygeal teratoma, one case of isomerism and one case of conjoined twins (Fig. 1) genitourinary, 3 (2%) head and neck, 29 (20%) multiple anomalies and 23 (16%) other.

Referring only to the definitive diagnosis, in 70 (49%) cases there was total agreement between US and autopsy (category A1). In 32 (22%) cases autopsy revealed other anomalies rarely detectable with prenatal ultrasound (category A2). Autopsy provided additional information about anomalies potentially detectable with second trimester US examination in 18 (12%) cases (category B). Finally, in 19 (13%) of cases some US findings were not

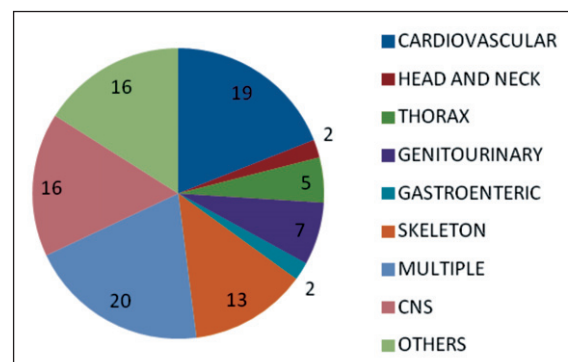


Figure 1. Division of malformations according to organ system.

verified at autopsy (category C) and in 5 (4%) cases there was a total disagreement between the two diagnosis (category D).

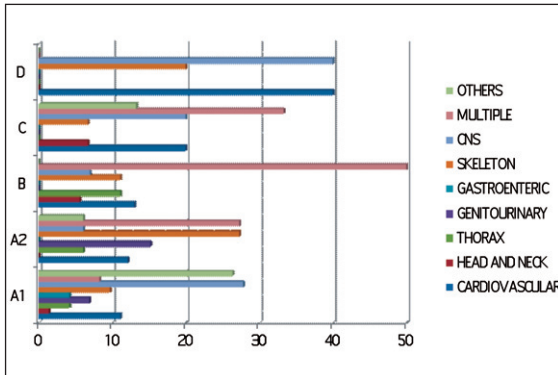


Figure 2. Division of different organs affected by malformations in the five categories.

Figure 2 shows distribution of the anomalies according to system involved in each of the five categories, giving an idea of which are the main organs represented in every category. CNS malformations and others like hydrops and cystic hygroma were mostly represented in category A1; in contrast, a lot of cardiovascular, scheletric and multiple anomalies were demonstrated only at autopsy (categories B and D). Category C included mainly complex, CNS and cardiovascular anomalies such as valve insufficiencies, pericardial and pleural effusions.

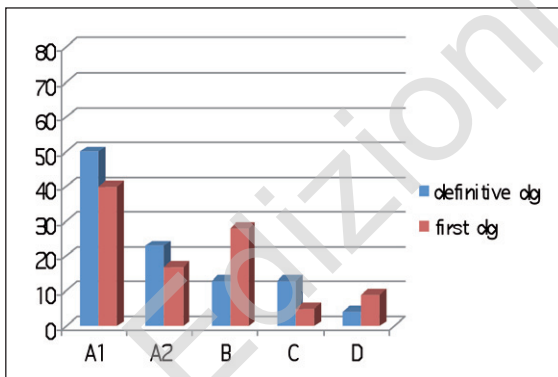


Figure 3. Percentage of degree of agreement between first and definitive diagnosis according to five classes.

Figure 3 shows the overall distribution of cases into the five categories, comparing the first diagnosis with that of our tertiary center. The difference between first and definitive diagnosis was statistically significant ( $p < 0.05$ ) just for categories B ( $p = 0.0019$ ) and C ( $p = 0.0046$ ). There was no significant difference between the two diagnosis for categories A1 ( $p = 0.23$ ), A2 ( $p = 0.46$ ) and D ( $p = 0.05$ ).

## Discussion

In our study, we compared prenatal ultrasound, as diagnostic tool to detect fetal malformations in the second

trimester of pregnancy, and autopsy to evaluate US diagnostic accuracy. Even if some defects could be observed now in very early pregnancy, the main method to detect fetal structural anomalies is the second trimester US examination, performed at about 20 gestational weeks.

Previously, several studies (4,5,12,7,13,14) stressed the correlation between US and pathology, often regarding fetal autopsy as the 'gold standard' and evaluating the 'specificity' and the 'sensitivity' of US towards autopsy. The 'sensitivity', in particular, does not seem to be elevated and it would not be over 40%. Those studies are very different in their inclusion criteria. Most of them included fetuses from all gestational weeks, spontaneous abortions and neonatal deaths (5,12,14-16,1). Only two studies specifically included fetal malformations detected at prenatal US in second trimester termination of pregnancy (15, 17). The conclusions of the study of Kanseen et al. showed discrepancies between US and autopsy findings in about 40% of cases, and that confirms the importance of pathological examination after every termination of pregnancy.

Most of these studies were retrospective in nature, as ours. In 2007 Akgun et al. published a prospective study concluding that evaluation of fetal autopsies following termination of pregnancy enables the diagnosis of pathologies undetected by prenatal US (18).

In the 2008 study by Antonsson et al. (2), US and autopsy were examined on the same methodological basis, in order to analyze the potential and limitation not only of US, but also of autopsy to reach a correct diagnosis. In that study it was pointed out that, in some cases, autopsy could have significant limitation, mainly concerning the diagnosis of CNS malformations. In fact, other studies demonstrate that postmortem magnetic resonance imaging (MRI) has an useful role in providing structural informations of the central nervous system in fetuses and stillbirth neonates (19, 20). We performed fetal MRI before the termination of pregnancy only in five cases because in all the others the patients had already decided to terminate pregnancy or the diagnosis was clear at US. In our study, we noticed an overall high degree of agreement between US definitive diagnosis and autopsy. In 71% of cases fetal anomalies detected at US were demonstrated also at autopsy (categories A1 and A2 together). Actually, if we consider the diagnosis from other structures, the degree of agreement decreased to 57% (categories A1 and A2 together). It is understandable that an US examination performed in a tertiary center, with machines of better quality, by experienced examiners and so with more regard to congenital anomalies, turns out to be more accurate than an examination performed in a not specialized structure.

Referring to the cases of total agreement (category A1), according to final diagnosis, the larger percentages concerned CNS malformations (71% of cases) and others like hydrops and cystic hygroma, for which we obtained a correspondence of 83%. Also cases of isolated gastroenteric anomalies, which included 3 cases of omphalocele, were fully confirmed by the pathologist, but this result are not so reliable because of the low numeric representation of this group.

In a few cases at autopsy the pathologist found out addi-

tional anomalies not really detectable at US (category A2). Most cases attributed to the category A2 were found among skeletal defects (27%), group of multiple malformations (27%) and genitourinary defects (15%). Two of these were represented by multicystic kidneys. Actually, renal cystic disease may be difficult to define on a scan because of a lack of amniotic fluid; moreover, the differentiation between infantile polycystic kidney disease and the cystic renal dysplasia may require histological examination (1).

It is known that in many cases of lethal skeletal dysplasia a diagnosis can be attempted prenatally, but confirmation is needed from autopsy and X-ray studies and these may change the suspected risk of recurrence from low to high (11).

In our study, we noticed that the isolated CNS malformation are not really represented in category A2 (6%), even if in the past a lot of studies stressed that the evaluation of fetal CNS by US is often limited (20). This result is very satisfactory, even though it is impossible not to consider the real difficulties in the study of the CNS, for the non-specific appearance of some anomalies, for technical factors that may complicate visualization of the brain near the transducer and of the posterior fossa (especially late in gestation), and because of subtle parenchymal abnormalities that frequently cannot be visualized (such as schizencephaly). Moreover US evaluation of the spine can be limited by oligohydramnios, maternal obesity and fetal position. Shadowing from the bony structure can also preclude a complete evaluation of the spinal cord and arachnoid sac (20). Also demonstration of corpus callosum on US is difficult. This leads to miss some diagnosis and because of those limitations a lot of studies have compared MRI and US for diagnosis of CNS anomalies, pointing out that MRI can be a good supplement to US in complicated pregnancies (19, 20).

In 12% of cases, autopsy provided additional information about clinically relevant anomalies not previously detected at US (category B). Additional pathological findings regarded in 29%, 31% and 33% of cases thoracic, multiple and head and neck malformations, respectively. Multiple malformations in particular were represented by arthrogryposis, cleft lip/palate, polydactyly and urinary tract defects like renal agenesis. Similarly to our results, in previous studies additional autopsy findings were obtained in 46% (4), 28% (14), 27% (21), 44% (22), 41% (23) and 40% (2) of cases and concerned above all complex anomalies (7).

In a 13% of cases some anomalies revealed at US were not verified at autopsy (category C). These cases concerned above all complex (33%), CNS (20%) and cardiovascular (20%) malformations.

There was total disagreement between US and autopsy (category D) in only 5 cases of 144 (4%) referring to the definitive diagnosis. This category included cardiovascular (2), CNS (2) and skeletal (1) malformations. One case of skeletal anomalies cannot be confirmed by autopsy because of fetal maceration, so that anomalies could not be identified. Also a case of holoprosencephaly was not observed by autopsy because of severe post-mortem autolysis of brain tissue. Another interesting case

was represented by a large meningocele that was clearly observed at US but, really surprisingly, was not demonstrated at autopsy.

Our findings are in complete agreement with what Antonsson et al. observed in their study (2). In this study it is pointed out that autopsy could not confirm some brain malformations that had been clearly detected at prenatal US because of extensive postmortem autolysis, probably related to long interval between fetal death and autopsy. Moreover it should be borne in mind that certain conditions of expulsion hinder examination as they involve an excessively long period of fetal retention leading to maceration in utero and tissue lysis, of brain tissue in particular (16).

So, it has been evidently shown that both US and autopsy may have some important limitations in diagnosing fetal abnormalities and that the two exams are complementary. Finally, from a comparison between first and definitive diagnosis, it has been pointed out that there was a statistically significant difference only for categories B and C. This means that a diagnosis made in a tertiary center is related to an higher detection rate of fetal malformations, mainly concerning functional defects, and to a smaller number of false negatives. This is very important because a correct diagnosis, in addition to a multidisciplinary counseling in a specialized center, affects the couple's decision to terminate pregnancy and maybe it could reduce the number of termination of pregnancy in the future.

## Conclusion

In conclusion, we think that our results demonstrate a tight relation between US prenatal diagnosis and autopsy findings, reflecting the potential and limitation of both techniques. The role of autopsy in complementing US to achieve an accurate diagnosis is undisputed. So autopsy examination is important in all cases of termination of pregnancy based on US findings, which are limited by much factors as the availability of appropriate machines and specialized examiners, in order to improve continuously the quality of prenatal diagnosis. But US sometimes could provide additional information, not subsequently confirmed by autopsy, that should not be always considered a false positive. We should begin to think that also autopsy, sometimes, could have limitations in detecting fetal malformations. US is a dynamic examination, appropriate to reveal functional changes not always detectable by autopsy, as pericardial and pleural effusions, flow inversion in aortic arch, valve insufficiencies. In these case it is reasonable that additional US information is not a false positive, but shows a major capacity of US in observing functional aspects not found by the pathologist.

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