Correlation between prenatal test results and foetal autopsy findings

Myrte Maessen & Beatrice C. van der Matten,
Medical students, Erasmus MC University Medical Center Rotterdam, the Netherlands
Correspondence: Myrte Maessen, email: 289389mm@student.eur.nl
Supervisors
Parita Tavare3, Professor in Medical Genetics
Rosete Nogueira2, MD, Specialist in Pathology
Yolande van Bever3, MD, Specialist in Clinical Genetics
Fred Petrij2, MD, PhD, Specialist in Clinical Genetics
2 CGC Genetics (Centro de Genética Clínica) Porto, Portugal
3 Department of Clinical Genetics at Erasmus MC University Medical Center, Rotterdam, the Netherlands

Abstract
Objective: To compare the results of prenatal screening and diagnostics to findings of the pathological examination after foetal demise. Our aim was to evaluate the additional value of the foetal pathological examination for final diagnosis and family counselling.

Study design: Retrospective cohort study of patient data obtained from all foetal pathological examinations performed at CGC Genetics in Porto during 2009.

Materials and methods: A database containing information on all 454 cases of foetal pathological examinations performed in 2009 was compiled. Of these, 161 cases met the inclusion criteria for analysis: information on foetal malformations found during prenatal ultrasound examination or with prenatal diagnostic techniques was available. To compare the autopsy findings to the results of prenatal screening/diagnostics, the cases were assigned to one of four subgroups according to their degree of concordance.

Results: Autopsy findings were concordant with prenatal results in all cases but one. Autopsy provided relevant additional findings in 29% of the cases and minor additional information in 11%. The rate of complete concordance was 59%. Apart from chromosomal abnormalities and single-gene defects, the rate of concordance was highest in cases of nervous system anomalies. In cases with cardiac, renal or digestive malformations, autopsy provided relevant additional information in more than half of the cases.

Conclusion: This study reinforces the value of foetal autopsy in medical genetic counselling after foetal demise by providing a diagnosis and by determining recurrence risk for future pregnancies.

Introduction
Major congenital malformations in foetuses make an important contribution to perinatal mortality rates. The prevalence of major congenital malformations in Europe is 23.8 per 1000 births. For live births this prevalence is 19.9 per 1000 births. The main causes of congenital malformations are structural heart disease (0.23/1000 births), chromosomal abnormalities (0.21/1000 births) and central nervous system defects (0.19/1000 births)(1).

During the last decade, prenatal screening methods and protocols have developed substantially. In most European countries, second trimester ultrasound screening is accessible to all pregnant women (2). Even earlier in the pregnancy, a calculation of the risk of Down’s syndrome can be made by combined ultrasonographic and biochemical screening methods.

When a congenital malformation or chromosomal abnormality is detected by prenatal ultrasound or diagnostic methods, many couples consider termination of the pregnancy. In order for couples to make a well-considered decision, they should be offered medical genetic counselling. During this counselling, a medical geneticist aims to provide information about the clinical features, causes and treatment of the malformation, explain the heredity of a genetic disease or recurrence risk of a malformation, and help the couple in the emotional process of decision making (3).

However, in some of the cases there is no definite prenatal diagnosis, for example when a cystic hygroma is seen on ultrasound, or when a cardiac malformation is suspected. In these cases, the consequences of the detected malformation for the child and its recurrence risk are not exactly known. Therefore, especially in these, but in general in all cases, pathological examination of the foetus (autopsy) after termination of pregnancy can provide essential information: a definitive diagnosis and its recurrence risk for future pregnancies (4,5).

Although identification of malformations by means of ultrasound screening and maternal serum markers testing has limitations, the rates of foetal autopsy are declining in Europe. Possible explanations for this decline could be the improvement in prenatal diagnosis techniques and adverse publicity on inappropriately conducted autopsies (4,6).

In our study we first processed the information from all foetal autopsies performed at CGC Genetics in 2009 into a database and selected cases for analysis. Subsequently, we compared the results of prenatal screening and diagnostics to the findings of the pathological examination of the foetus after termination of pregnancy, spontaneous pregnancy loss, intrauterine foetal death, stillbirth or early neonatal death. Our aim was to evaluate the additional value of the foetal pathological exam for final diagnosis and family counselling.
We addressed the following research questions: a) Does foetal autopsy provide additional information, b) is this information relevant in terms of changing the recurrence risk and therefore, is autopsy needed for proper family counseling? c) Should autopsy be performed in all cases of foetal demise?

**Materials and methods**

We retrieved all foetal pathology cases of 2009 from the archive at CGC Genetics and compiled a database using the Microsoft Access database programme. This resulted in information on 454 cases.

**Inclusion and exclusion criteria**

Cases of foetal autopsy after termination of pregnancy due to medical reason (TOP), spontaneous pregnancy loss, intrauterine foetal death (IUFD), stillbirth or early neonatal death, for which records on foetal malformations found by prenatal screening or diagnostic tests were available, were included. Cases for which no clinical information about prenatal results was available were excluded. Cases with only non-foetal abnormalities detected by ultrasound, such as placental abnormalities, amniotic liquid aberrations and suspected molar degeneration, were excluded. When only an ultrasound finding was described that could be a physiological variation, e.g. increased nuchal translucency, the case was also excluded.

**Analysis**

Analysis was performed by establishing groups of cases according to the organ system of the foetal malformation (organ system subgroups were derived from the EUROCAT-classification (1)). Each case was studied separately, describing what information was known prenatally and after autopsy. We determined whether the information that could be given during medical genetic counselling of the parents was different after autopsy. This information comprised the definitive diagnosis, its clinical features and lethality, its recurrence risk for future pregnancies and whether the parents and other family members should undergo clinical examinations or genetic tests to exclude or prove a specific origin of the foetal malformation.

The information about clinical features, origins and recurrence risks was retrieved from the books ‘Oxford desk reference, clinical genetics’ by Firth & Hurst (7) and (1)Practical genetic counselling, by Harper (8), from medical genetic information databases GeneReviews (9) and OMIM (Online Mendelian Inheritance in Man) (10) and from medical studies found in the PubMed international database of literature.

According to the degree of concordance between prenatal and autopsy results, the cases were assigned to one of the four following subgroups:

1. Complete concordance
2. Partial concordance, additional information from the autopsy was not clinically relevant
3. Partial concordance, with clinically relevant additional findings from the autopsy (change in recurrence risk or clinical consequences for the couple; e.g. genetic tests, cardiac ultrasounds, blood perfusion tests)
4. Discordance

All cases were reviewed by both researchers. If we had any doubt about the assignment of a case into one of the subgroups, then the case was discussed with the pathologist and/or with the clinical geneticist to determine the effect of the additional findings on the recurrence risk, and thus, the consequences for genetic counselling. Statistical analysis was not performed; the results will be displayed descriptively.

**Analysis of subgroups**

To display the results, percentages of cases assigned to the four subgroups are shown, followed by a subdivision into organ systems. The organ system subgroups with the largest numbers of cases and some particularly interesting cases will be discussed in more detail.

**Results**

**Figure 1 - Overview of inclusion of cases**

In 293 cases, no information or insufficient information was provided on the results of prenatal examinations. Most of these concerned spontaneous abortions at short gestational age. Probably, no prenatal screening had been performed as yet in these cases. The remaining 161 cases were included for analysis (Fig. 1). In 111 cases, a foetal malformation was detected by ultrasonographic examination; in 75 cases an abnormality was found by prenatal diagnostic techniques.

**Figure 2 - Distribution of the type of pregnancy outcome in the 161 included cases (TOP: termination of pregnancy for medical reason, IU: intrauterine)**

Prenatal findings

**Ultrasoundographic examination**

The cases were categorized into organ system subgroups according to the anomalies found during ultrasound examination. When malformations in more than one organ system were identified, an additional second and third organ system could be identified. In Table 1, only the organ system of the primary malformation is shown.
Original Contribution

Table 1 - Organ system of the primary malformation found by prenatal ultrasound

<table>
<thead>
<tr>
<th>Organ system (primary malformation)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td>32</td>
<td>28.8</td>
</tr>
<tr>
<td>Heart</td>
<td>18</td>
<td>16.2</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Digestive system</td>
<td>4</td>
<td>3.6</td>
</tr>
<tr>
<td>Abdominal wall</td>
<td>8</td>
<td>7.2</td>
</tr>
<tr>
<td>Urinary system</td>
<td>9</td>
<td>8.1</td>
</tr>
<tr>
<td>Limb</td>
<td>5</td>
<td>4.5</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Other anomalies</td>
<td>33</td>
<td>29.7</td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
<td>100</td>
</tr>
</tbody>
</table>

The subgroup ‘other anomalies’ contains abnormalities that did not fit into one specific organ system, e.g. lymphatic anomalies (cystic hygroma) and intrauterine growth restriction.

Prenatal diagnosis
In 75 cases, a prenatal diagnosis was made by karyotyping, FISH (Fluorescent In Situ Hybridization)- screening for aneuploidies or molecular diagnosis of a specific disease or mutation. In 71 cases (94.7%), a chromosomal abnormality was found, e.g. a trisomy, triploidy or duplication. In the remaining 4 cases, a single-gene defect was identified, e.g. a homozygous deletion in the SMN1-gene (Survival Motor Neuron 1-gene), causing muscular atrophy.

Autopsy findings
The cases were categorized into organ system subgroups according to the anomalies found during autopsy. When malformations in more than one organ system were identified, an additional second and third organ system could be classified. In Table 2, only the organ system of the primary malformation is shown. The diagram (Fig. 3) also shows the organ systems of the additional malformations.

Figure 3 - Diagram showing the distribution of the organ systems of the primary and additional malformations found at autopsy

Table 2 - Organ system of the primary malformation found by prenatal ultrasound

<table>
<thead>
<tr>
<th>Organ system (primary malformation)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td>30</td>
<td>18.6</td>
</tr>
<tr>
<td>Heart</td>
<td>17</td>
<td>10.6</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Digestive system</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>Abdominal wall</td>
<td>5</td>
<td>3.1</td>
</tr>
<tr>
<td>Urinary system</td>
<td>9</td>
<td>5.6</td>
</tr>
<tr>
<td>Genitalia</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Other anomalies</td>
<td>9</td>
<td>5.6</td>
</tr>
<tr>
<td>Chromosomal abnormality</td>
<td>71</td>
<td>44.1</td>
</tr>
<tr>
<td>Single-gene defect</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>Placental cause</td>
<td>6</td>
<td>3.7</td>
</tr>
<tr>
<td>Unclassified</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Total</td>
<td>161</td>
<td>100</td>
</tr>
</tbody>
</table>

In the case that could not be classified, the autopsy was severely limited due to a papyraceous foetus.

Subgroups of concordance
According to the degree of concordance between prenatal and autopsy results, the cases were assigned to one of the four subgroups of concordance (as described in Materials and methods).

Table 3 - Assignment of the cases into subgroups of concordance, per organ system of the primary malformation found at autopsy

<table>
<thead>
<tr>
<th>Organ system (Primary malformation)</th>
<th>Subgroup of concordance (n)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td>16 5 9 - 30 (18.6)</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>5 2 9 1 17 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Respiratory system</td>
<td>1 1 - 2 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Digestive system</td>
<td>- - 4 - 4 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Abdominal wall</td>
<td>1 3 1 - 5 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Urinary system</td>
<td>2 2 5 - 9 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Genitalia</td>
<td>- 1 - - 1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>- - 2 - 2 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Other anomalies</td>
<td>1 5 3 - 9 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Chromosomal abnormality</td>
<td>65 - 6 - 71 (44.1)</td>
<td></td>
</tr>
<tr>
<td>Single-gene defect</td>
<td>4 4 - - 4 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Placental cause</td>
<td>- - 6 - 6 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Unclassified</td>
<td>- - - - 1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Total number of cases</td>
<td>95 18 46 1 161 (100)</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td>59.0% 11.2% 28.6% 0.6% 100%</td>
<td></td>
</tr>
</tbody>
</table>

Discordance
In one case, prenatal diagnosis and autopsy results disagreed (concordance subgroup 4). At amniocentesis, a trisomy 15 was detected, but cytogenetic analysis after termination of the pregnancy revealed a normal 46,XX karyotype. This pregnancy was initially a twin pregnancy, with early loss of one foetus. Possibly, the material retrieved at amniocentesis came from the vanishing twin. During autopsy of the second foetus, tetralogy of Fallot, pyloric stenosis and pulmonary immaturity were found. No tissue of the first foetus was found during autopsy.
Description of largest organ system subgroups

Chromosomal abnormality

A chromosomal abnormality was found in 71 cases. Trisomy 21 was the most common result. In 41 cases, abnormalities were found at prenatal ultrasound. The most commonly detected anomalies were: increased nuchal translucency, cystic hygroma and fetal hydrops/anasarca. In the remaining 30 cases, it was unclear to us whether an ultrasound was performed. The diagnosis was prenatally detected in 66 cases. The type of prenatal diagnostic technique was either amniocentesis (38 cases) or chorionic villous sampling (6 cases). In 22 cases, the PND-type was unknown.

During autopsy, foetal anomalies related to the karyotype were identified in all cases. In 65 cases (91.6%), autopsy did not provide additional information (concordance subgroup 1). In 6 cases (8.5%), autopsy provided relevant additional information: 5 diagnoses of chromosomal abnormality and 1 Parvovirus B19 infection as the cause of intrauterine foetal death.

Nervous system

In 30 Cases, nervous system anomalies were identified during autopsy. The most common findings were acrania/anencephaly and holoprosencephaly.

Prenatal ultrasound was performed in all cases. In only one case, no nervous system anomaly was seen on the ultrasound. In this case a cystic hygroma and anasarca were found. In 2 cases an amniocentesis excluded a chromosomal abnormality.

Additional anomalies were found during autopsy in several cases: renal anomalies, abdominal wall defects, cardiac malformations, limb anomalies and genital anomalies. In 5 cases, the additional information was not clinically relevant (concordance subgroup 2). In 9 cases, the autopsy revealed additional information that changed the recurrence risk (concordance subgroup 3): specification of the diagnosis in 3 cases, identification of aqueduct stenosis as a cause of hydrocephalus/ventriculomegaly in 4 cases and discovery of relevant additional malformation in 2 holoprosencephaly cases.

Remarkably, all 9 cases of acrania/anencephaly were detected by prenatal ultrasound.

Heart

A congenital heart malformation was found during autopsy in 17 cases. The most common diagnoses were hypoplastic left heart syndrome and ventricular septal defect.

In one case the mother was affected: she had mitral valve prolapse. The foetus was found to have mitral valve dysplasia and agenesis of the right hand. Maternal diabetes was present in two other cases.

Prenatal ultrasound was performed in 16 cases. In 13 cases, a cardiac malformation was detected. Additional anomalies identified were: facial clefts, digestive system malformations, musculoskeletal and limb anomalies and ‘other’ anomalies (e.g. foetal hydrops). In the other 3 cases, a limb malformation, a cystic hygroma with anasarca and an echogenic intracardial focus were found.

Prenatal diagnostic techniques were performed in 5 cases, of which one was abnormal: 47,XX,+15 (this was the discordant case).

In 5 cases, complete concordance between prenatal and autopsy results was found. Of these, 4 cases were of hypoplastic left heart syndrome, the 5th case involved polymalformation syndrome. In 9 cases, additional anomalies were found that changed the recurrence risk (concordance subgroup 3), most often involving definition of the cardiac diagnosis.

Discussion

In our study, data from all 454 cases of foetal pathological examination performed at CGC Genetics in 2009 were collected in a database. Our analysis included 161 cases for which information on results of prenatal examinations was available, regardless of gestational age or type of pregnancy outcome.

We believe that in all events of foetal demise, at any time during pregnancy and for every pregnancy outcome, family counselling is essential for the parents’ emotional and psychological management of the situation and for their knowledge and understanding of the malformation and its recurrence risk in future pregnancies. Therefore, we have combined the foetal pathological perspective with the viewpoint of medical genetics.

Several recent studies have examined the correlation between prenatal screening/diagnosis results and autopsy findings. Like our study, most of these studies were retrospective. Overall, the studies were initiated from a neutral perspective, evaluating the value of screening methods as well as foetal autopsy. Since our cases came from a foetal pathology archive, they were reviewed from a pathological perspective.

As in most earlier studies, we classified our 161 included cases into subgroups of concordance between prenatal and autopsy results, where 95 Cases (59%) were assigned to subgroup 1 (complete concordance). This percentage is similar to results found in other studies that describe a rate of complete concordance that varied from 36-64% (4,5,6,11-15). Of our cases, 18 (11%) were classified as subgroup 2 cases (minor additional findings). This is slightly less than the 17-39% described by other studies (4,6,12,15). On the other hand, our percentage of subgroup 3 cases (relevant additional information) is slightly higher than in other studies; 29% (46 cases) versus 13-27% (4,6,16,17). This shift may be explained by our broad definition of ‘relevant additional information’. For instance, cases in which placental pathology was found were assigned to subgroup 3, because this was an indication for maternal screening for haematological abnormalities.

In cases of chromosomal abnormalities or single-gene defects, the rate of concordance was the highest, because most of these abnormalities were diagnosed prenatally. Apart from chromosomal abnormalities and single-gene defects, the rate of complete concordance was highest in cases of nervous system anomalies. But for cardiac, renal and digestive malformations, autopsy provided relevant additional information (concordance subgroup 3) in more than half of the cases. Autopsy was also essential in the diagnosis of placental pathology.

In other studies, the rate of discordance varied from 0% to 3.6% (6,11-16). Of our cases, only one was assigned to this subgroup.

Unfortunately, information about maternal clinical or obstetric history provided by physicians was not always complete and consistent. We expected the physicians to have provided the information if it was abnormal or of particular interest for pathology or medical genetics. But it is possible that we missed relevant data. This demonstrates the importance of the provision of all relevant clinical information by physicians, on the one hand for their colleagues in pathology and medical genetics, and on the other hand for medical research. It also shows a disadvantage of the retrospective study design: if it had been a prospective study, physicians would be instructed on what clinical information to provide. Another disadvantage of the retrospective design is the possible bias in selecting and excluding the cases while already knowing the autopsy results.
In the foetal pathological examination at CGC Genetics, radiography is not standard. But in case a skeletal anomaly was identified prenatally, or was suspected at macroscopic examination, the foetus was taken to a nearby centre for radiography. (Figure 4)

Finally, our study was limited by our restricted knowledge of the Portuguese language and training in medical genetics. We avoided translation errors by asking for explanations from the laboratory staff or the pathologist. Moreover, classification of the cases into subgroups is a subjective process. We have tried to be consistent by carefully writing down our definitions and by rechecking all cases before retrieving the results. If we had any doubt, we consulted the pathologist and/or the medical geneticist.

Conclusion and recommendations

Our results demonstrate the value of autopsy for medical genetic counselling on the recurrence risk of foetal anomalies, especially in cases not prenatally diagnosed with a genetic abnormality. Moreover, ultrasonographers, clinicians performing prenatal diagnostic tests and laboratories performing karyotyping and genetic tests benefit from autopsy results as a quality control. Therefore, we recommend that foetal autopsy be performed in all cases of foetal demise in which no chromosomal abnormality or single-gene defect was detected by prenatal diagnosis.

Furthermore, we would like to emphasize the importance of good communication between the physician, who should provide consistent and complete clinical information, and the pathologist, who needs to give clear instructions, e.g. on how the foetus should be preserved before it arrives at the pathology laboratory.

References


Figure 4 - X-ray image and photograph after medical termination of the pregnancy of a foetus diagnosed with thanatophoric dysplasia. Note the short limbs, bowing of femur and humerus and hypoplastic thorax, typical for this musculoskeletal malformation. (Pictures: Pathology laboratory, CGC Genetics, Porto, Portugal)