Morphopathologic Features of Fetal Appendages in Fetal Distress

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ABSTRACT Fetal growth depends on the integrity of fetal appendages. The aim of the study was to reveal the possible correlations between different morphological changes of each of the three fetal appendages (placenta, umbilical cord and amnios) and the presence of one of the two aspects of fetal distress (FD) (acute or chronic). Placental weight and type of fetal appendage pathological process were assessed on 116 patients whose newborns had fetal distress. The results of our analysis allowed us to conclude that umbilical cord pathology was not the main cause of FD as one might think at first sight but placental pathology, which was the main factor in both the intrauterine growth retardation (IUGR) subgroup as placental insufficiency as well as the acute fetal distress (AFD) group as premature detachment of normally inserted placenta (PDNIP). Associations of several pathological processes of fetal appendages were rare, usually leading to the onset of IUGR.

KEY WORDS Fetal distress, Fetal appendages, Morphology

Introduction

Fetal autonomy in terms of oxygen does not normally exceed two minutes [Fournié et al. 1995]. Fetal distress is defined as a decrease in oxygen and an accumulation of carbon dioxide resulting in a state of "hypoxia and acidosis" during intrauterine life. Depending mostly on the onset, there are two distinct entities of fetal destress, also with different clinical behaviors, diagnostic algorithms and therapeutic approaches.

AFD is defined as a serious disturbance of fetal oxygenation that occurs during pregnancy. The two most important consequences of this are intrapartum or neonatal death and cerebral motor infirmity (the cerebral palsy described by Anglo-Saxon authors) [Boog 2001]. AFD may occur at any time during a pregnancy, previously considered within physiological parameters. In most cases, however, AFD occurs during labor [Colette 2000]. AFD may be linked to a variety of circumstances, including placental lesions that may affect the transfer of oxygen or knotting of the umbilical cord (UC) and UC twining.

IUGR is a syndrome characterized by the unattainment of the normal growth potential of the fetus, leading to the attainment of the maximum intrauterine development [Malhotra et al. 2006; Wang et al. 2006]. It represents a major risk factor for increased mortality, perinatal and neonatal morbidity and number of stillborn [Claussen et al. 1999]. This pathological process, often associated with malplacentation, also causes significant morbidity, 10% of children with low weight presenting mental disabilities, with a higher rate of failure in school and a further 5% showing chronic neurological sequelae [Gaffney et al. 1994; Parkinson et al. 1986].

After eliminating malformations and genetic causes, placental insufficiency remains the major cause of IUGR [Amu et al. 2006]. Therefore, obstetricians, pediatricians and pathologists should be familiar with the routine diagnosis of fetal appendages and especially the placenta so that the data exchange between the specialists mentioned can provide, in as many cases, helpful diagnostic information critical to newborn care [Khong et al. 1986].

The examination and assessment of placental integrity have a major and immediate impact in the delivery room because they can reveal information that may be important in immediate and long term management of both the mother and the fetus. For example, placentae with a thickness of less than 2.5 cm are associated with IUGR [Kuhlmann and Warszof 1996]. Cord abnormalities are clearly associated with a number of intrauterine factors and a number of consequences, some of them not becoming obvious until much later during the child’s life.

Based on these premises, we intend to make an analysis of morphological changes of fetal appendages encountered in cases diagnosed with FD and also of possible correlations between types of lesions identified and the two forms of FD. Our approach was further motivated by the small number of references directly related to the relationship between the onset of FD and the
presence of a pathological process in one of the fetal appendages, in both romanian and international literature.

**Material and Methods**

**Materials**

The basis of this study was represented by a group of 116 patients in which FD was related to a pathological process of fetal appendages.

The batch was divided into three groups according to the fetal appendage that induced FD. The main pathological process located in the fetal appendages was taken into account, whether it was single or associated with another pathological process of the appendages. Each of the three groups was divided into two subgroups, depending on the type of FD identified in newborns, namely fetuses with AFD and fetuses with IUGR (Table 1).

**Table 1: Studied batch and subgroups**

<table>
<thead>
<tr>
<th>1. Studied batch</th>
<th>1. IUGR</th>
<th>1. AFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Studied batch (Presence of FD)</td>
<td>2. 32</td>
<td>2. 90</td>
</tr>
<tr>
<td>3. (116 cases) - 122 fetuses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. - Group I - Placental Pathology</td>
<td>3. 28</td>
<td>3. 53</td>
</tr>
<tr>
<td>5. (75 cases) - 81 fetuses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. - Group II - Umbilical Cord Pathology</td>
<td>4. 11</td>
<td>4. 35</td>
</tr>
<tr>
<td>7. (46 cases/fetuses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. - Group III - Pathology of the Amnios</td>
<td>5. 0</td>
<td>5. 4</td>
</tr>
<tr>
<td>9. (4 cases/fetuses)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data sources from which the material was selected for the study were: medical records of all cases included in the study (clinical observation charts of pregnant women and newborns, records of surgical protocols, birth and histopathological records).

Materials were represented by the selected data set from medical documents as well as tissue samples and fragments of amniotic membranes that were processed histologically.

**Methods**

For data collection, "database" files were created on the computer in which parameters that were to be studied were introduced, namely: Placental weight and Type of placental pathologic process.

The evaluation of placental weight implied the distribution into 8 weight groups (Table 2), the lowest weight, highest weight, average weight, standard deviation, variation coefficient and confidence interval were also determined.

**Table 2: Placental weight groups**

<table>
<thead>
<tr>
<th>1. Weight Group</th>
<th>1. Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. PW1</td>
<td>2. W &lt; 200 g</td>
</tr>
<tr>
<td>3. PW2</td>
<td>2. 200 g &lt; W &lt; 300 g</td>
</tr>
<tr>
<td>4. PW3</td>
<td>2. 300 g &lt; W &lt; 400 g</td>
</tr>
<tr>
<td>5. PW4</td>
<td>2. 400 g &lt; W &lt; 500 g</td>
</tr>
<tr>
<td>6. PW5</td>
<td>2. 500 g &lt; W &lt; 600 g</td>
</tr>
<tr>
<td>7. PW6</td>
<td>2. 600 g &lt; W &lt; 700 g</td>
</tr>
<tr>
<td>8. PW7</td>
<td>2. 700 g &lt; W &lt; 800 g</td>
</tr>
<tr>
<td>9. PW8</td>
<td>2. 800 g &lt; W &lt; 900 g</td>
</tr>
</tbody>
</table>

Amniotic membrane fragments were subjected to conventional histological processing techniques (fixation and paraffin wax embedding) followed by sectioning and HE staining.

The collected data were processed using the Microsoft Excel module of the Microsoft Office 2003 Professional software pack.

**Results**

Fetal distress was induced by a variety of pathological processes affecting one or more of the fetal appendages.

Placental impairment was the most frequent finding in both groups defined, but only in half of the of cases in the subgroup with the AFD as compared with two thirds in the IUGR subgroup.

Note also that cord pathology was due to the AFD in a significant proportion - 38% of all cases - three times more common than the subgroup with IUGR (which represented 12.5% of cases) and that in the subgroup with IUGR, associations of fetal appendage impairment were the second most frequent, with 21.8%, more common than the pathology of the UC (Diagram 1).

**Diagram 1: Types of pathologic aspects of fetal appendages**

It should however be noted that in all 7 cases the association was about a lesion of the UC simultaneous with a placental pathologic process.

It should also be noted that impaired fetal membranes, either isolated (three cases) or associated with another pathological process of the appendages (one case) was seen only in the AFD subgroup.
Pathology of the Amnios

The amnios (A) was the site of a FD generating pathological process only in four cases. In three of these cases, it was the single impaired fetal appendage.

Two of these cases had hydramnios. The cardinal sign of fetal distress was the absence of fetal heart beat. The parturient spontaneously gave birth to a stillborn male weighing 2100 g, with anencephaly. In the second case with hydramnios, the cardinal sign of FD was the presence of heart beat accelerations, tachycardia. The parturient spontaneously gave birth to a male fetus weighing 3600 g. The third case was that of a 32 year old pregnant woman, admitted for inflammatory symptoms in the genital area and loss of amniotic fluid. The cardinal sign of AFD was fetal bradycardia. The patient has a spontaneous abortions at 28 weeks of a male fetus weighing 900 g with APGAR 2. Histopathological examination of fetal appendages revealed the diagnosis of chorioamniotitis (Figure 1).

In the fourth case, in addition to the pathology of membranes represented by an oligoamnios, there was also an associated pericervical twined UC. Fetal distress was signaled by both severe bradicardia-type changes in fetal cardiac activity, and the presence of meconial amniotic fluid. The parturient spontaneously gave birth to a male fetus weighing 3200 g.

Umbilical Cord Pathology

The UC was the site of a pathological process that induced fetal destress in 46 cases. In most of these cases (37 cases – 80%) this was the only pathological process leading to the onset of FD. In 9 cases, in addition to the pathological process of the UC, FD syndrome was also determined by a second pathological process located in the fetal appendages. In eight of these cases, the accompanying pathology was placental insufficiency, its morphological expression being the identification after birth of multiple foci of limestone impregnations in placental parenchyma. In the previously mentioned ninth case, the pathological process of the UC was associated with the presence of olygoamnios.

In most cases (38 out of 46), the cord anomaly was represented by the twining of the UC. Four cases had true knots, two cases had a short UC and in two cases we observed an association between two anomalies of the cord, namely the presence of a true knot with a „scarf” twining of the UC and a pericervical twining of the UC.

In the AFD group, isolated twined UC was the most common cord lesion while in the IUGR group, the percentage of cases where cord lesions were associated either with other lesions of the cord or other injuries or fetal appendages exceeded 60% (Diagram 2).

![Diagram 2: Types of pathologic aspects of Umbilical Cord in studied groups](image)

In both groups the dominant type of cord twining was the pericervical one. It should be noted however that in the IUGR group, the „scarf” twining of the cord was present in a significant percent (30%), as compared to the AFD group, where the prevalence of this type was below 10% (Diagram 3).

![Diagram 3: Types of Umbilical Cord twining in studied groups](image)
twinings in the AFD subgroup with AFD had double winding pericervical twining. In one case of this subgroup, we encountered even a triple winding loose twining (Diagram 4).

**Diagram 4: Types of Umbilical Cord pericervical twining in studied groups**

True knot (TK) (Figure 2) was encountered in a minority of cases (6/46). In half of these cases the knot was solitary (Figure 2). In the rest of the cases, the knot was accompanied by a double winding loose pericervical twining of the UC, a simple loose “scarf” twining and a placental insufficiency syndrome. Most cases with TK - five - belonged to the subgroup of fetuses with AFD.

Short cord was seen only in two cases, both belonging to the subgroup of fetuses with AFD.

**Figure 2: True Knot - 38 weeks of gestation, AFD, Spontaneous eutocic delivery, Female fetus, 3600 g**

**Placental Pathology**

**Placental Weight**

Almost three quarters of the placentae examined had weights between 300 and 700 g. The dispersion interval ranged between 150 and 830 g, with an averaged weight of 455.33 g. Concentration interval of most cases defined by the standard deviation ranged from 315 g to 595 g (Table 3).

**Table 3: Statistical analysis**

<table>
<thead>
<tr>
<th>Statistical parameter</th>
<th>Entire batch</th>
<th>AFD</th>
<th>IUGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wmin</td>
<td>150</td>
<td>150</td>
<td>230</td>
</tr>
<tr>
<td>WMax</td>
<td>830</td>
<td>830</td>
<td>680</td>
</tr>
<tr>
<td>MW</td>
<td>455.33</td>
<td>478.72</td>
<td>384.06</td>
</tr>
<tr>
<td>Std. Dev.</td>
<td>140.05</td>
<td>138.27</td>
<td>100.80</td>
</tr>
<tr>
<td>V.C. (%)</td>
<td>30.76</td>
<td>28.88</td>
<td>26.25</td>
</tr>
<tr>
<td>C.I. (95%)</td>
<td>430.48 – 480.18</td>
<td>449.50 – 507.94</td>
<td>349.14 – 418.99</td>
</tr>
</tbody>
</table>

In the AFD subgroup, the situation is somewhat similar to that of the entire batch, except that all values are shifted to the right. In the IUGR subgroup, the situation is different. Thus, the dispersion interval is narrower (between 230 and 680 g), but shifted to the left. The mean weight is about 70 g smaller than that calculated from the entire group and even if the standard deviation has a lower value (100.8 vs. 140.05), the range of concentration of cases is significantly shifted to the left (between 283 g and 485 g) (Table 3), emphasizing that placental weights in this subgroup were generally lower.

**Placental Pathological Processes**

Of the 75 cases in which placental pathological processes are involved in the onset of FD, placental impairment was the only cause of FD in 67 cases. There were, however, 8 cases in which there was an associated pathological process which was located in the UC (twinning of the UC in 7 cases and a TK in one case). Associations of pathological processes of fetal appendages were seen, with one exception, in cases with IUGR (Diagram 5). While in the AFD the placental pathologic process was identified antepartum in almost two thirds of cases, in the IUGR subgroup, its antepartum diagnosis was possible in less than 20% of all cases (Diagram 6). The remaining cases were labeled as placental insufficiency syndrome which has been cleared after delivery, following gross morphological examination of the placenta in the delivery room.

**Diagram 5: Types of Placental Pathology (PP) in studied groups depending on presence of association**
The dominating pathological processes diagnosed antepartum were implantation defects of which the most common was PDNIP with formation of retroplacental hematomas of various sizes (17 cases). Positioning vices of the placenta followed, represented by different variants of placenta praevia (9 cases) and placenta accreta (5 cases). In four cases we found placental infarction. Of these cases, only 6 belonged to the IUGR subgroup, that is 2 cases with PDNIP, 2 cases with placenta praevia and 2 cases with placental infarction (Diagram 7).

Of the 40 cases with an antepartum diagnosis of placental insufficiency syndrome, 37 cases were pregnancies with single fetus and 3 cases were twin pregnancies.  

**Cases With Single Fetus**  

**Macroscopic features of the placenta.** The most frequent pathological macroscopic feature was the presence of calcification foci within placental parenchyma and especially at the surface of cotyledons. In over half the cases where they have been identified, they were associated with other pathological changes of the placenta.

The next pathological macroscopic aspect was the atrophic appearance of the placenta, with reduced size and weight, with obvious ditches between cotyledons, with a firmer texture of placental parenchyma, due to the presence of fibrous traveae of variable thickness and dispersion, especially visible on cotyledon crossection. The atrophic appearance was also associated with other gross pathological aspects in almost half of the cases in which it was identified.

**Figure 3: (a) - Placental Calcifications; (b) - Placental Atrophy**

Another aspect was the fatty appearance. This was observed less frequently, especially in larger placentae, and was often associated with other pathological macroscopic appearances.

**Diagram 9: Types of placental macroscopic pathological features in studied groups**

AFD was associated most frequently with the presence of placental calcification foci, and secondly, with the fatty appearance. In contrast, IUGR was associated most often with placental atrophy (Atph), isolated or associated with limestone impregnation (Diagram 9).
components, most often similar to those present in the third trimester of pregnancy. Thus, villous structures were turgid and dense as opposed to those from term pregnancies, separated by wider intervillous spaces, but not as those from term pregnancies. The double cellular layer seen in villous structures during the second trimester of pregnancy was less well represented and the identification of the cytotrophoblast was very difficult. The villous syncytiotrophoblast was thin and, in many cases, clusters of syncytial cells called "nodes" were visible within the villous syncytiotrophoblast (Figure 4).

*Figure 4: Secondary and tertiary chorial villi. Thin syncytiotrophoblast. Syncytial „Nodes“.*

In cases with microscopically atrophic placentae clusters of fibrillar collagen structures could be observed between villi.

**Cases with Twin Pregnancies**

All three cases with twin pregnancies belonged to the AFD subgroup. Macroscopic evaluation of placentae revealed the discrepancy between placental development and fetal request, while microscopic evaluation showed incomplete development similar to that described above.

**Discussions**

Analysis of the results obtained from the assessment of data related to the two morphological parameters taken into account – the type of pathological process located in the fetal appendages and placental weight – in conjunction with the two varieties of fetal insufficiency syndrome - AFD and IUGR, led to some interesting observations.

**Pathology of the Amnios**

Of the four cases with amniotic membrane pathology, one with chorioamnionitis comes to stress that the inflammatory processes of fetal appendages represent a category of pathological process that should not be overlooked as they can lead to fetal and neonatal morbidity and mortality.

There is a variety of mechanisms by which these inflammatory processes can lead to death; however, they can be summarized into four distinct classes: (a) involvement of the placenta and membranes with loss of function, (b) induction of premature labor and premature birth, (c) release of inflammatory mediators leading to fetal organ damage and (d) transplacental infection of the fetus [Redline 2004].

**Pathology of the Placenta and Fetal Distress**

Placental pathology has been identified as the cause of placental insufficiency syndrome onset in just over half the cases studied but its involvement in the pathogenesis of the two types of FD was different, being the main determinant in the IUGR subgroup (responsible for the development of the syndrome in two thirds of all cases).

Our study revealed also an otherwise logical fact, that is, the placental tissue mass, quantified morphologically by determining the weight, may be one of the determinants of FD onset.

Thus, it was observed that lightweight placentae generated RCIU. Therefore, given that modern investigative techniques currently allow an antepartum morphological assessment of the placenta, the IUGR diagnosis should not be established only postpartum.

In determinism of cases in which the placental pathological process could be identified antepartum, PDNIP had a central role place in the pathogenesis of AFD, followed by other implantation defects and in particular the various versions of positioning defects (placenta praevia). Special mention must be made for placenta accreta, in which case, due to the intrapartum diagnosis, a direct correlation AFD/placental pathology is not possible, because the diagnosis is intrapartum, but one can only make observations.

Regarding the label "placental insufficiency syndrome" attributed to all cases in which an antepartum placental pathological process that can be held liable for the onset of one of the types of FD could not be identified, postpartum macroscopic and microscopic morphological examination could identify changes to justify the existence of the syndrome.

Thus, macroscopic examination revealed limestone impregnation, Atph or, in other words, a small disproportionate placenta in relation to fetal weight (even if its appearance was normal), or a "fatty" appearance, in other words, the "dystrophic" placenta.
Microscopic examination provided a different set of arguments to support the diagnosis of placental insufficiency syndrome, namely: more dense and turgid villous structures, with wider villous spaces, a cytotrophoblast that is more difficult to identify, thinned syncytiotrophoblast with clusters, syncytial cell "nodes", fibrillar collagen structures and clusters between villi.

**UC Pathology and FD**

Although, at first glance, one might think that UC pathology should be the main cause of FD, our study revealed an interesting aspect, that is the identification of pathological processes of the UC in only one third of cases as the main determinant for the onset of one of the types of FD.

Of all pathological processes involving the UC, the twining of the UC came out to be by far the most frequent one. In this regard, two interesting aspects are worth mentioning.

The first is that, within the group with UC pathology, isolated twinning of the UC, whether single or multiple, was responsible for the onset of FD in most cases of the AFD subgroup of this batch, and only in one third of all cases in the IUGR subgroup.

The second aspect that attracted our attention was that the UC twinnings lead to AFD even if they are loose (55% of cases) and even if they are single.

**Associations between Pathological Processes of the Appendages and FD**

Associations of several pathological processes involving the fetal appendages which led to the onset of FD were rare, less than 10%, but it is interesting to note that most of the cases in which such combinations were identified developed IUGR.

**Conclusions**

Our study showed that UC pathology was not the main cause of FD, as one might think at first sight. Twinning of the UC was the most common pathological process involving the UC. The isolated form, either single or multiple, was responsible for the onset of FD in most cases of the AFD subgroup and an aspect which keeping in mind is that our data analysis showed that UC twinning can lead to AFD even if loose or single. However, the looseness of the UC twinning directly correlates with the severity of changes in fetal cardiac activity, bradycardia, a sign of advanced AFD, being more common in cases with tight UC twining.

Placental pathology was the main determining factor in the IUGR subgroup, being responsible for syndrome development in two thirds of the cases.

Placental tissue mass, quantified morphologically by determining the weight, may be one of the determinants of FD onset. Thus, lightweight placentae generated IUGR. Therefore, given that modern investigative techniques currently allow an antepartum morphological assessment of the placenta, the IUGR diagnosis should not be established only postpartum.

PDNIP had a central role in the pathogenesis of AFD. In the case of placenta accreta, because the diagnosis is established intrapartum, a direct correlation AFD/placental pathology is not possible, because the diagnosis is intrapartum, but one can only make observations. PDNIP and placental infarction induced a relatively early onset of AFD.

Associations of several pathological processes involving the fetal appendages were rare, less than 10%, which led to the onset of IUGR.

**References**


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Abbreviations

P  Placenta
P-PV  Placenta Praevia
P-A  Placenta Accreta
PP  Placental Pathology