Etiopathogenetic, clinical and histopathological aspects regarding the involvement of dental focal infection in premature births with fetal hypotrophy

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Abstract
The study conducted on a total of 1344 preterm births, of which 403 hypotrophic fetuses births (between 2010–2012 within the Maternal Clinics of Craiova, Romania), studied the involvement of dental inflammatory infections in the chorioamnionitis onset. The possibility of transferring germs, toxins and degraded materials into the blood flow, and them entering the chorioamniotic structures is quite a common issue. Subclinically often evolving chorioamniotic membrane and its existence is clearly established after birth by histopathological and bacteriological examinations, being partially responsible for the growth delay of the conception product. Our study revealed this fact, by using clinical examinations, ultrasound exams, bacteriological determinations of the amniotic fluid and the placenta, alongside the histopathological examinations. The chorioamnionitis inflammatory process is responsible for premature birth, through a high synthesis of interleukins (IL) and prostaglandins, causing uterine contractions. Our IL-6 dosage determinations show its growth that can be considered a prediction marker for preterm birth.

Keywords: dental outbreak, fetal hypotrophy, premature birth.

Introduction
Dental infectious pathology is quite common in pregnancy due to pregnancy specific changes (immunological, hormonal and metabolic changes) [1]. Pregnancy gingivitis is present in over 50% of pregnant women. Dental focal infection [2–4], through its diversity of clinical and organic symptoms, is not often considered by obstetricians.

The dental infection (dental abscess, tooth cavities, gum pus pockets) determines the disease focal, which may present acute or chronic (light) symptoms, in relation to the affected organ. In many cases, the alarming symptoms (fatigue, low fever, myalgia) are not taken into consideration as these are similar to pregnancy signs.

There are very few data in the literature involving the dental focal infection in fetal hypotrophy and premature births. We wanted to emphasize the role of dental infection in premature births and fetal hypotrophy.

A fetus is considered hypotrophic when its weight or size is below a limit set for a reference population. Hypotrophy has multiple causes (diseases of the mother and fetus, poor nutrition and infectious, vascular, tumoral, uteroplacental processes). The clinical and ultrasound observation of the fetus, amniotic fluid and placenta, and its comparison with known diagrams helps us determine the fetal hypotrophy diagnosis and its evolution [5]. Premature birth is defined as pregnancy termination between 28–37 weeks of gestational age, having as a result the birth of a fetus less than 2500 g. The World Health Organization (WHO) has decreased the gestational age, setting other criteria as well [5, 6]. Premature births in Romania represent around 10% of the total births; around the world, it varies between 4% (Belgium) and 34% (Pakistan).

Among the etiological factors in premature birth and fetal hypotrophy, we quote [5, 6]:

- maternal factors: maternal diseases such as hypertension, metabolic diseases, infectious diseases, genetic diseases;
- placental factors: placental insufficiency, premature rupture of membranes, etc.;
- socioeconomic factors: mother’s poor nutrition, lack of hygiene, etc.

The mechanism by which dental infectious pathology triggers premature birth and fetal hypotrophy is complex, either by hyperthermia or by ionic enzymatic metabolic changes, but the most serious one is the blood entering of germs and their toxins, of the infected damaged tissues that can reach the placenta, the amniotic fluid or the fetal membranes, thus determining chorioamnionitis [7].

Chorioamnionitis is defined as the inflammation of the chorioamniotic structures, the route of contamination could be ascending, with a cervicovaginal starting point, especially after membrane rupture, but the infection can reach the amniotic cavity through transplacental blood contamination, possibly from the dental focal infection [8–10].
Chorioamnionitis may clinically manifest as severely acute, but most often it evolves with mild symptoms, often leading to premature birth and fetal hypotrophy. Even in the absence of germs, their toxins or damaged tissues can alter the uteroplacental exchanges with repercussions on the developing fetus. In chorioamnionitis, the placenta and the membranes lose their luster, the surface presents small abscesses, necrosis, while vessels present thrombosis, the leukocyte infiltration being a massive one [11, 12].

Materials and Methods

Taking into consideration the role of infectious dental pathology (dental focal infection) in fetal hypotrophy and premature births, we performed a statistical study upon the presence of dental diseases in a group of 1344 premature births of which 403 with hypotrophic fetuses, delivered in the Maternal Clinics of Craiova, Romania over the past three years. At the same time, we excluded the involvement of other clearly causal factors.

In order to emphasize the implication of clinical dental focal infections, we determined the presence of dental germs, and also the presence of germs in the amniotic fluid, in the placenta, in the cervicovaginal area, keeping in mind the presence of the same germs in the above mentioned structures. For determining the presence of germs in the dental infection and in the amniotic fluid, there were performed inclusions from the amniotic fluid and dental infection on a gelose blood blade with a 15 cm diameter and dental infection on a gelose blood blade with a 15 cm diameter, highlighting the number of colonies after 24 hours (the number of colonies being a test for the infection stage).

The colonies were harvested for germ detection. In pregnant women with clear dental focal infections, IL-6 (high in infectious processes) was dosed in the amniotic fluid and dental infection on a gelose blood blade with a 15 cm diameter and dental infection on a gelose blood blade (the number of colonies being a test for the infection stage).

The diagnosis of possible premature birth, premature birth, fetal hypotrophy, dental outbreak, chorioamnionitis was determined based on the clinical examination, ultrasound exam, biological blood samples, determination of germs and histopathological examination. The studied groups were compared with the reference groups of normal pregnant women. The results were interpreted by using the Student’s t-test.

The histopathological study was performed on eight placentas with dental hypotrophy resulted from premature births, presenting macroscopic chorioamnionitis aspects.

The eight pregnant women were diagnosed with dental infections and a multitude of chorioamnionitis phenomena. The pregnant women were hospitalized in the Clinic of Obstetrics and Gynecology, within the Emergency County Hospital of Craiova, Romania.

The important placental tissue fragments were subjected to conventional histological processing techniques (including paraffin embedding), serial sections being performed from each block.

For the placentas taken from pregnancies with macroscopic chorioamnionitis, there were used the Hematoxylin–Eosin (HE) and trichromic Goldner–Székely (GS) stainings. The histopathological aspects were studied by using the Olympus CX31 microscope, with a ×4, ×10, ×100 magnifying glass. The most suggestive images were taken with Lite View Pro digital camera. Then, we processed the data by using the Analysis Pro software and Photo Camera Lite v. 1.1 ACDSee 4.0 software.

Results

Out of the 9465 births that took place over the past three years within the Maternal Clinics of Craiova, there were recorded 1344 premature births, of which 403 were prematurely born with hypotrophic fetuses (Table 1).

<table>
<thead>
<tr>
<th>Year</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total births</td>
<td>3415</td>
<td>3106</td>
<td>2944</td>
<td>9465</td>
</tr>
<tr>
<td>Premature births</td>
<td>498</td>
<td>456</td>
<td>390</td>
<td>1344 (14% of all births)</td>
</tr>
<tr>
<td>Premature births with hypotrophic fetuses</td>
<td>149</td>
<td>124</td>
<td>130</td>
<td>403 (30% of all premature births)</td>
</tr>
</tbody>
</table>

According to the table, there were a large number of premature births (14%), of whom 30% were hypotrophic.

As the figures vary slightly from one year to another, we chose only one year for the study regarding the causes of premature births with hypotrophic fetuses (Table 2).

<table>
<thead>
<tr>
<th>Causes</th>
<th>Total premature births (390)</th>
<th>Total premature births with hypotrophic fetuses (130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical maternal factors</td>
<td>164 (42%)</td>
<td>70 (55%)</td>
</tr>
<tr>
<td>Feto-placental factors</td>
<td>66 (16.9%)</td>
<td>29 (22%)</td>
</tr>
<tr>
<td>Social and economic factors</td>
<td>40 (10.2%)</td>
<td>20 (15%)</td>
</tr>
<tr>
<td>Unknown factors</td>
<td>120 (30.7%)</td>
<td>11 (8.4%)</td>
</tr>
</tbody>
</table>

The most common causes are due to maternal medical factors (hypertension, infectious diseases, etc.). However, there is a large percentage of fetoplacental factors.

Regarding the major dental pathology of pregnant women with premature births in a year (390), 38% had pregnancy gingivitis, 16% tooth decay and 15% periodontal disease. There were a number of 130 premature births with hypotrophic fetuses and the percentage of dental outbreaks implicated is clearly shown in the table below (Table 3).

<table>
<thead>
<tr>
<th>Total premature births with hypotrophic fetuses</th>
<th>Clearly Implicated Dental infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>130</td>
<td>32 (24.6%)</td>
</tr>
</tbody>
</table>

We subsequently highlighted the germ colonies and identified the germs in the dental infection, in the amniotic fluid and cervicovaginal germs, and isolated the common germs in these areas (Table 4).

The cervicovaginal germs were the same as those present in normal pregnant women without ruptured membranes. IL-6 values are shown in Table 5.
Table 4 – Germ colonies grown from amniotic fluid cultures and dental infections and common germs implicated

<table>
<thead>
<tr>
<th>Stained pregnancies with premature birth and hypotrophic fetuses (20 cases)</th>
<th>No. of colonies in dental infections</th>
<th>No. of colonies in amniotic fluid cultures</th>
<th>Common germs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Staphylococcus, Streptococcus, Escherichia coli, Proteus enterobacteria</td>
</tr>
<tr>
<td>Control group (20 cases)</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Table 5 – Amniotic fluid IL-6 values in pregnant women with premature hypotrophic fetuses (p<0.01)

<table>
<thead>
<tr>
<th>Premature births with hypotrophic fetuses – in pregnancies with dental infections (10 cases)</th>
<th>60 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies without dental pathology – births with eutrophic fetuses (10 cases)</td>
<td>52 ng/mL</td>
</tr>
</tbody>
</table>

Histopathological examinations of placentas and fetal membranes are presented in the images below (Figures 1–8) and commented upon in the discussion section.

Discussion

The percentage of premature births in the studied area over a period of three years was of 14%, and of these 30% were premature fetuses with hypotrophy (Table 1).

The percentages are higher than the average. One possible explanation would be the poor nutrition of pregnant women in the area, the living conditions and their insufficient medical surveillance.

The causes of premature births and fetal hypotrophy are complex, but our study shows the predominance of pregnancy-induced or associated hypertension (see Table 2), which has a negative impact on the placental exchange. We should also keep in mind other pregnancy-associated diseases, but also social and economical factors, the amniotic fluid and placental diseases, etc.

The data are similar to those quoted in the literature [5, 6]. Literature quotes 30–40% unknown factors in the etiology of premature births. We believe that the oral-dental infectious pathology may be implicated in investigating these unknown factors as an oral-dental examination is rarely performed by obstetricians. Our selection went beyond these facts and, through clinical, bacteriological and histopathological investigations and after excluding other factors, it has revealed that dental outbreak is clearly involved in the premature birth of hypotrophic fetuses (32 cases, 27%) (Table 3).

Figure 1 – Thirty-six weeks placenta with chorioamnionitis. Trichromic GS staining, ×40.

Figure 2 – Overview of fetal membranes in amniotic sac infection. Massive inflammatory infiltrate. HE staining, ×100.

Figure 3 – Thirty weeks pregnancy placenta with chorioamnionitis hyaline villi. Trophoblastic necrosis. Area of obstructed vessels. HE staining, ×100.

Figure 4 – Thirty-two weeks pregnancy placenta. Fetal cord Wharton’s jelly inflammatory infiltrate. Thrombi of umbilical vessels. HE staining, ×40.
It should be emphasized that tooth infection creates a sepsis especially during pregnancy, because of immunosuppression and metabolic ionic, enzymatic and hormonal changes that is why the clinical aspects may have different clinical signs, sometimes mild or missing.

Dental pathology causes poor mastication, vomiting with repercussions on the growth and development of the fetus [7], but even more serious is the transfer into the blood flow of the germs and their toxins from the dental outbreak, of the degraded tissue, of breakdown products which reach the utero-placental structures in the amniotic fluid, determining infection and chorioamnionitis, respectively (Table 4).

The data on chorioamnionitis are found in the literature [6, 9, 13–15] but there are few data about the implication of dental focal infection. This damaging of the utero-placental structures implicitly affects the growth and development of the conception product. The clinical forms of chorioamnionitis are rarely acute; they generally evolve with mild symptoms or they are even asymptomatic [15]. Dental outbreak is often involved in the chorioamnionitis with mild symptoms or asymptomatic one, as presented in the clinically monitored cases, by detection of germs and macroscopic histopathological and histological placenta examinations (see Figures 1–8).

The uteroplacental infection of the fetal amniotic fluid very often leads to premature delivery and fetal hypotrophy. In premature birth, there is well known that the affected chorioamniotic structures release A2 phospholipase and interleukin (see Table 5), which play a role in the synthesis of prostaglandins that cause uterine contractions [16, 17]. Germs and toxins from dental focal infection enter the blood every now and then and, thus, this leads to an inconsistent bacterial infection.

Pregnant women with active dental infections are 10 times more prone to premature births with hypotrophic fetuses and 30 times to chorioamnionitis [10]. In addition to the existing colonies of bacteria in the amniotic fluid and in the dental plaque, we must mention that the vaginal flora studied in pregnant women with dental diseases and intact membranes showed no major change from the normal vaginal flora. While discussions are upon the fact that the amniotic infection is often parting from the vagina, we have avoided women with premature several hours ruptured membranes. The germs transfer through intact amniotic membranes is very rare. The pregnant women with dental infections included in the study had intact membranes until delivery.

The placentas and amniotic membranes studied after premature births with hypotrophic fetuses, in which there
was involved either a clear or possible asymptomatic chorioamnionitis (20 placentas) reveal the macroscopic aspect of infected placenta and membranes, in that the placentas and membranes lose their characteristic luster. Umbilical cords are frail and edematous, with areas of thrombosis and necrosis. The placentas studied under the microscope demonstrate the infectious process, starting from leukocyte infiltration up to subchorionic abscesses and necrosis. The vascular changes consist of thrombosis and images of thrombophlebitis and arthritis, around which there occur various stages of necrosis.

Conclusions

The bacterial flora in the dental plaque, by determining the dental septic focal infections and by bacteremia causes uteroplacental septic infections, often-fetal hypotrophy, and premature delivery. The germs, toxins and the damaging material of the dental infection can enter the blood stream and reach the chorioamniotic structures, the amniotic fluid and the fetus, determining chorioamnionitis and fetal distress. Chorioamnionitis often evolves with mild symptoms or asymptomatically, but it affects the fetus that can evolve with growth delay. The uterine decidual cells, the amniotic cells under the action of pathogenic agents secrete phospholipase and interleukin that lead to a prostaglandin increase, substances that often cause agents secrete phospholipase and interleukin that lead to premature delivery.

Histopathological examinations of the placenta and of the amniotic membranes with the presence of chorioamnionitis, even in the absence of clinical symptoms, represent strong elements that involve the dental infectious disease in fetal hypotrophy and premature births. Our study shows a decrease of the percentage (30–40%) of unknown factors in determining premature birth and recommends obstetricians to also take into consideration the oral-dental pathology in everyday medical practice.

Author contribution

All authors have equally contributed to this paper.

References


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