Maternal factors in early neonatal death: the need to train first-contact health personnel

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Clinical history
The patient is a newborn male of 7 days of age who was born after 35 gestation weeks and was the product of the mother’s first gestation. Family history includes a 29-year-old mother who is a homemaker. She admits to occasional smoking and alcohol consumption. During pregnancy she did not smoke or consume alcohol. The father is a 34-year-old construction worker who also admits to occasional smoking and alcohol consumption and is otherwise healthy. The remaining clinical history is not relevant to this case.

The patient was a native and resident of the State of Mexico. His home was without electricity or drainage services. There were two dogs and four cats living in the home. He was breastfed every 3 h. The mother received prenatal care along with folic acid and multivitamin supplementation. Threatened miscarriage was documented during the first trimester and was managed with complete rest. Mother presented cervicovaginitis during the last trimester; however, she received no treatment. The child was born through eutocic delivery at week 35 of gestation due to early membrane breakage. Weight of the newborn was 1900 g and length was 44 cm. Apgar score was 7 and the newborn presented with spontaneous crying and breathing.

The patient was seen at the Hospital Infantil de Mexico Federico Gomez (HIMFG) because of left equinovarus foot. During consultation he presented reduced suction, adynamia and sudden apnea. Physical exploration revealed a male newborn with apparent age equal to chronological age, normotensive anterior fontanel (4 x 3 cm), pointed posterior fontanel, normal cardiac sounds, without chest excursion movements. Abdomen was soft and depressible with hepatic border (3 x 3 x 3 cm) below the right ribs. Limbs were hypotonic and hypotrophic, osteotendinous reflexes +/+++ +, 3/5 muscular force in four limbs, and preserved sensitivity and primary reflexes were present.

Patient was intubated and we found unbalanced metabolic acidosis with 8.8 bicarbonate and hyperlactatemia. He was managed with saline solution, norepinephrine and midazolam. The patient remained stable for 8 h and presented 59% oxygen desaturation, cardiorespiratory arrest, bleeding through oral-tracheal tube, rectum and venodissection site. Patient did not respond to resuscitation maneuvers.

Dr. Amalia Pastor Peralta (Pediatric Services)
We treated a 35-gestation-week newborn and conducted neonatal screening for hypothyroidism, which was negative.
Radiological Findings

Dr. Nora Isela Moguel Molina (Imaging Services)

The radiological file contains three studies. The first study was carried out on June 5, 2008 and was a chest/abdomen x-ray demonstrating that the left hemothorax was completely clouded and mediastinal structures were retracted. Right hemothorax revealed generalized interstitial prominence and endotracheal cannula resting in the distal site of the main right bronchus. Liver silhouette was increased, displacing intestinal loops (Figure 1). The second X-ray film was taken during that afternoon with left hemothorax re-expansion. Endotracheal cannula was found 2 cm from the carina of the trachea (Figure 2). The third study was carried out on June 6, 2008 showing no differences compared to the previous study and without pleural effusion.

Discussion

Dr. Teresa Murguia Peniche (Neonatology Department)

We treated a 35-gestation-week newborn male with weight and size appropriate to chronological age. He was born as a result of a high-risk pregnancy and delivery should have taken place at a tertiary care hospital with close postnatal follow-up and a visit 48-72 h after discharge to rule out dehydration, jaundice or omphalitis. A study on the risks associated with pregnancies of between 34 and 36.6 gestation weeks revealed an increased mortality rate up to 11 times higher than that associated with full-term newborns.\(^1\) The patient was referred to the HIMFG because he presented equinovarus foot without urgency data from the referral hospital, which indicates the need to train medical and paramedical personnel to identify such data. Upon admission he presented apnea, which rapidly evolved to shock, disseminated coagulation and death. Data that support shock profile are 3-sec capillary fill, neurological alterations such as apnea, hypotonia, hyporeflexia and metabolic acidosis. Possible causes of this profile are as follows:

- Bacterial sepsis
- Congenital cardiopathy
- Metabolic diseases such as hematochromatosis or organic acidemia
- Serious bleeding caused by K vitamin deficiency

Differential Diagnosis

Bacterial Sepsis

Sepsis is defined as a clinical syndrome characterized by signs of infection and systemic inflam-

![Figure 1. Simple thorax-abdominal x-ray from June 5 at 11:27 shows full left hemothorax clouding with mediastinum retraction. Right hemothorax with generalized prominence of interstitium. Endotracheal cannula shows distal end in main right bronchus. Liver appears enlarged.](image1)

![Figure 2. Second thorax-abdominal X-ray from June 5 at 18:40 shows left hemothorax re-expansion. Endotracheal tube is in proper place. No infiltrates or pleural effusion are revealed.](image2)
inflammatory response. This patient had bandemia and required intubation. Clinical profile evolved to shock. Traditionally, neonatal sepsis has been classified as either early or late. Early neonatal sepsis is generally very severe, fulminating and multisystemic, occurring during the first days of life. Generally there are obstetric complications, as in this case, such as premature membrane rupture, prematurity and chorioamnionitis. Bacteria are acquired from the mother’s vaginal canal. Late neonatal sepsis may occur from the fifth day of life, although onset in most cases is after the first week of life. Obstetric complications may also be present and etiological agents may be bacteria from the vaginal canal or community-acquired or from contaminated equipment.2

It is very likely that this newborn presented late neonatal sepsis. The main risk factors for sepsis are low weight at birth and prematurity. A study by Melamed et al. demonstrated late-premature newborns present 10 times the risk of infection than full-term newborns.3 Therefore, it is important to closely watch these newborns. Other antecedents that support bacterial sepsis are premature rupture of membranes, fetidness from umbilical cord and clinical profile. In this case, fetidness from umbilical cord was a very important sign of possible blood contamination by bacteria. Necrotic tissue and thrombosed vessels in umbilical cord are an excellent bacterial culture that rapidly disseminates through blood vessels. Infection can also advance through abdominal wall fascia or through peritoneum and produce septic thrombi. In this case there were no apparent data of fasciitis and there was only abdominal distension.

Infectious agents and their products are able to release pro- and anti-inflammatory cytokines as well as activating the coagulation cascade responsible for systemic inflammatory profile and disseminated intravascular coagulation (DIC).

The most frequent etiologic agents, especially those with fulminating effects, are gram-negative bacteria such as Escherichia coli, Enterobacter sp., Klebsiella sp. and Pseudomonas sp. There have been cases due to coagulase-positive staphylococcus infection, especially those associated with osteoarthritis or omphalitis and coagulase-negative staphylococcus infection in case of nosocomial infections.4

It is worth mentioning the findings by Flavia Rossi et al. who reported that up to 44% of Staphylococcus aureus strains in Mexico are methicillin resistant; this should be considered when using empiric antibiotic treatment under different clinical situations.5

Findings of bandemia and thrombocytopenia support this diagnosis. Blood culture was negative; however, autopsy series with confirmed sepsis have demonstrated that blood culture sensitivity to detect bacterial sepsis is only 82%,6 so this result should be ruled out. Furthermore, it has been described that blood culture may result as negative when taken late during clinical profile or when blood volume is insufficient.7

Herpes simplex infection
Another possibility is herpes simplex virus (HSV) infection. These infections can present in three forms:

- Local to central nervous system (CNS)
- Local to skin, eyes and mucous
- Disseminated

This may be a form of DIC with possible involvement of CNS according to neurological data at physical exploration: hypotonia, hyporeflexia, dilated pupils and lethargy. This is supported by incubation period from the clinical profile (7-10 days) and its severity with rapid evolution to shock, history of cervicovaginitis and 12-h premature membrane rupture. This is also compatible when the mother presents herpes simplex genital infection and membrane rupture >4 h increases
the risk of neonatal transmission, negative blood culture result, immunofluorescent HSV2 detection in umbilical stump and hyperproteinemia with erythrocytes in cerebrospinal fluid (CSF). According to the experience of the Collaborative Antiviral Study Group (CASSG) to which we belong to, 186 newborns with HSV were studied in the U.S., Canada and Mexico. Of these, one third presented disseminated disease and only 60% presented skin lesions (therefore, absence of skin lesions does not rule out this diagnosis). Furthermore, between 60% and 80% of the cases of neonatal herpes have no history of genital herpes infection in the mother.8,9 Contrary to this diagnosis is having a diagnostic test without 100% specificity that did not find increased transaminases or pneumonia at admission. Neonatal herpes patients usually die because of these problems and DIC.9,10 DNA for HSV should have been searched for using PCR test in blood and CSF and through viral culture in conjunctiva, skin, urine and CSF. Another diagnostic element that helps clarify this diagnosis is brain magnetic resonance imaging where alterations have been described in inferomedial section of the temporary lobe.

Congenital cardiopathies
Congenital cardiopathies can also begin with apnea and evolve into shock. Cardiopathies present during the first week of life are chiefly dependent on conduction and left-ventricle hypoplasia has been frequently associated with shock during the first week of life. Onset is generally associated with hypoperfusion, oxygen desaturation, tachycardia and tachypnea with or without heart murmur. Clinical profile is practically indistinguishable from other causes of shock and, therefore, current recommendations include initial prostaglandin therapy until demonstrating the absence of conduction-dependent cardiopathy.11 Contrary to this diagnosis is the absence of high ventilation requirements to maintain low CO₂ levels because this pathology generally results in passive and active lung congestion.

Innate errors of metabolism
Another possibility is innate errors of metabolism that quickly evolve into shock. Owing to the contribution of Dr. Velasquez et al. from the National Institute of Pediatrics (INP), we know these problems are far more frequent than we thought. Their incidence can reach 1/1000 live newborns in Mexico.11 The main problems are organic acidemia because of persistent acidosis, urea-cycle problems, etc. Therefore, it is necessary to consider organic acids, ammonium and extended neonatal screening under these circumstances even when the patient has received blood transfusion. Because this case presented a fulminating evolution, there was no time to study this aspect; however, it is important to keep it in mind and perform all diagnostic tests from symptom onset.

Finally, we should consider vitamin K deficiency and bleeding for differential diagnosis, perhaps involving CNS, with hypovolemic shock data. In these cases, there are initial alterations of prothrombin time (PT), but if bleeding is considerable other DIC data may be added.

This patient presented hyperbilirubinemia and because of initial hemoglobin levels and no apparent incompatibility with blood group and Rh, this may not have been hemolytic. It is possible that it was related to dehydration, shock and possible sepsis.

Regarding treatment, the clinical history makes it difficult to establish how quickly the patient was managed, but it was evident that resuscitation maneuvers were indicated with fluids up to 50 mL/kg and there was no restoration of circulation (persistent slow capillary filling, altered neurologic state and metabolic acidosis). Treatment was initiated with 6 mg/kg/min glucose solution. Guidelines from the American College of Critical Care Medicine recommend beginning with 8 mg/kg/min to avoid hypoglycemia12 as in this case, which was detected late during evolution. Norepinephrine was administered but not recommended as routine therapy. New shock management guidelines
recommend using dopamine first and if there is no response then begin epinephrine administration because most shock cases in newborns are cold. Prostaglandin therapy should have been attempted before ruling out conduction-dependent cardiopathy. Very high dosages of midazolam were administered.

It is important to remember that newborns in this period are in transition from fetal to postnatal life; therefore, persistent pulmonary hypertension is easily developed. Consequently, an echocardiogram should have ideally been carried out and this procedure should be available 24 h/7 days per week in ICU and emergency rooms. If persistent pulmonary hypertension was present, the patient should have received nitric oxide within the first hour of shock diagnosis. If echocardiogram was unavailable, preductal and postductal oxygen saturation should have been measured: a difference >5% is a guideline for this diagnosis. Obviously, the response was not timely. Finally, the patient experienced increasing sudden oxygen desaturations. In this scenario, we should rule out the following: hemothorax, hemopericardium, pneumothorax, increased intra-abdominal pressure, equipment malfunction or endotracheal cannula displacement. If the aforementioned complications are discarded, hydrocortisone or thyroid hormone therapy should be started. It is unclear if these complications were ruled out in this case.

In this patient, because of hemorrhage predisposition, dilated pupils and lack of respiratory automatism, CNS hemorrhage should have been ruled out with possible involvement to brain stem. In summary, this was a newborn from a high-risk pregnancy who suffered a possibly septic shock (difficult to differentiate if etiology was viral or bacterial) and who experienced complications with DIC and possible hemorrhage to CNS.

This case exemplifies the current status of mortality associated with neonatal sepsis in Mexico. Deaths from this cause have doubled in the last 30 years.13 Public health measures should be implemented to detect high-risk newborns, indicate alarm data to parents and healthcare personnel and check all newborns between 48 h and 72 h of discharge to detect alarm data.

Dr. Casasola (Virology Laboratory)
Viral isolation was requested from cerebrospinal fluid postmortem. This test provides us scarce information. It is possible to carry out a polymerase-chain reaction test in the HIMFG, which is a more sensitive and specific test. Also, tests for HVS1 and HVS2 were requested from umbilical cord samples. These tests have very little sensitivity. Specificity can be high. In this case, we observed a positive result that may have been associated with sample contamination.

Dr. Rocio Pena Alonso (Pathology Department)
Postmortem study revealed a weight of 2200 g for an expected weight of 3172 g with length appropriate for chronological age (43.5 cm, expected length 44 cm). Patient showed development with peri-oral and nailbed cyanosis. We found a 1-cm surgical wound on the right neck associated with central venous catheter placement. We found bilateral pneumothorax. During cavity exploration, we found 15 cm³ hemorrhagic liquid in the pericardial cavity, 15 cm³ hemorrhagic liquid in the right pleural cavity, 10 cm³ exudate effusion in the left pleural cavity and 15 cm³ xanthochromic fluid in the peritoneal cavity. Neck dissection revealed hematoma in soft tissues extending towards right and left pleura. Lungs were the most affected organs (Figure 3). Prematurity complications and their treatment regarding lungs include hyaline membrane disease, bronchopulmonary dysplasia and interstitial emphysema. There was poor fetal to neonatal transition requiring intra-alveolar fluid replacement by air and surfactant, which will keep an appropriate tension in alveolar surface. These lung alterations represent the leading causes of morbidity and mortality in premature children whose lungs frequently present an immature morphology and inappropriate.
functionality. In our patient, pulmonary pleural surface presented accentuation of lobular pattern. Histological section revealed a spongy surface with dilation of air spaces. Mucous from trachea and main bronchi showed edema and focal ulceration. Histologically, lungs presented variable bronchiole obliteration and bronchiolectasis, type 2 pneumocyte hyperplasia, atelectasis and vascular wall thickening. There was focal hemorrhage (Figures 4 and 5). Umbilical cord presented intense inflammatory infiltrate chiefly comprised of polymorphonuclear leukocytes (Figure 6). Liver presented sinusoidal congestion, extramedullary hematopoiesis and mild intracellular cholestasis. Thymus presented reduced lymphoid elements and dense eosinophil material at the lumen of Hassall’s corpuscles. Digestive tube opening revealed the presence of 20 cm³ blood at stomach, duodenum and ileum. Smooth muscle at stomach, esophagus and ileum presented contraction bands. There was intra-parenchymatous hemorrhage in testes and coagulative necrosis with focal

Figure 3. Lung cut surface shows accented lobule pattern with small dilations giving a spongy aspect. Heart shows no structural alterations.

Figure 4. Histologically, lungs show immaturity composed by thickened alveolar septum mostly covered by cube-like cells. Dilation of alveolar spaces is variable. No infection data were observed.

Figure 5. Areas of focal pulmonary hemorrhage.

Figure 6. Umbilical cord soft tissues around vessels show intense polymorphonuclear leukocyte infiltrate creating small abscesses.
hemorrhage in adrenal cortex. Brain base showed subarachnoid hemorrhage at occipital lobes and cerebellum (Figure 7).

Our patient was a premature newborn with low weight for gestational age (actual weight 1910 g vs. expected weight 2382 g according to Usher and McLean) with early neonatal death. Antecedents included first pregnancy with premature rupture of membranes, omphalitis and sepsis.

Premature rupture of membranes is often found with very young or older mothers, hypertension, infections, anemia, thrombotic dysfunction, obesity, diabetes, cervical incompetence and multiparity in the group of maternal factors associated with neonatal death. Final postmortem diagnoses are shown in Table 1.

Table 1. Final postmortem diagnoses

<table>
<thead>
<tr>
<th>Primary disease</th>
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<tbody>
<tr>
<td>Premature newborn with low weight for gestational age</td>
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<td>(observed 1910 g vs expected: 2382 g, Usher &amp; McLean)</td>
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<tr>
<td>Early neonatal death</td>
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<tr>
<td>Premature membrane rupture</td>
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<td>Cervicovaginitis</td>
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<th>Concomitant alterations</th>
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<tr>
<td>Omphalitis</td>
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<td>Immature lungs</td>
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<tr>
<td>Bilateral pneumothorax</td>
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<tr>
<td>Bilateral hemothorax (15 cm³ right /10 cm³ left)</td>
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<tr>
<td>Hemopericardium (10 cm³)</td>
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<tr>
<td>Intracellular cholestasis</td>
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<td>Hematoma in soft tissue of neck due to central venous catheter</td>
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<td>Left equinovarus foot</td>
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<th>Shock and sepsis anatomic data</th>
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<tr>
<td>Acute thymus involution</td>
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<tr>
<td>Hypoxic-ischemic myopathy</td>
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<tr>
<td>Acute hypoxic encephalitis</td>
</tr>
<tr>
<td>Recent hemorrhage in esophagus, lungs, kidneys, testes, parenchyma, choroid plexuses and subarachnoid space</td>
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<tr>
<td>Coagulative necrosis in adrenal cortex</td>
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<tr>
<td>Contraction bands in smooth muscle from stomach, small intestine and colon</td>
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<tr>
<td>Blood in digestive tube, stomach and ileum, 29 cm³</td>
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<th>Postmortem cultures</th>
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<tr>
<td><em>Escherichia coli</em> in blood culture, colon and left lung</td>
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<tr>
<td><em>Enterococcus faecium</em> in blood culture</td>
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<th>Cause of death</th>
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<tr>
<td>Sepsis from <em>Escherichia coli</em> and <em>Enterococcus faecium</em></td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
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Figure 7. Brain stem showing subarachnoid hemorrhage.
Maternal factors in early neonatal death: the need to train first-contact health personnel

Dr. Amalia Pastor Peralta

As a conclusion, I would like to propose the following:

• It is essential to inform and instruct parents and relatives in alarm signs before discharging newborns to home.
• It is important to carry out full physical exploration to every patient, including those who arrive to intensive care areas in critical condition and the need to have first-contact healthcare personnel able to recognize alarm signs in newborn patients.

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References