

PREGLED LITERATURE – REVIEW ARTICLE

Perinatal Autopsy and Placental Examination an Important Contribution to Diagnosis and Follow-up after a Fetal Loss

Prenatalna autopsija i ispitivanje placente kao važan doprinos dijagnostici i praćenju nakon gubitka ploda

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Summary Fetopathology is the study of fetal deaths or eventually developmental anomalies occurring during early or late pregnancy. The major objectives of the fetal or perinatal autopsy are to evaluate gestational age, document growth and development, detect congenital abnormalities, analyze clinical diagnosis and treatment and determine the cause of death and possible recurrence risk. It must be associated to the analysis of the placenta to respond to questions concerning the cause of death or risks of recurrence in a subsequent pregnancy. The analysis follows a well-developed protocol and the results have to be interpreted by a multidisciplinary group including the obstetrician, the geneticist, the neonatologist and the pathologist.

Key words: fetal autopsy, cause of death, placental examination

Sažetak Fetopatologija je nauka o razvojnim anomalijama fetusa ili fetalnoj smrti koje se javljaju tokom rane ili kasnije trudnoće. Osnovni cilj fetalne ili perinatalne biopsije je da se utvrdi gestacijska starost, utvrdi stepen razvoja ploda, utvrdi prisustvo kongenitalnih anomalija, analizira klinička dijagnoza i sprovedena terapija, kao i da se utvrdi uzrok smrti i mogući rizik od ponovljene fetalne smrti. Obavezno se ispituje i stanje placente, kako bi se utvrdio uzro fetalne smrti i rizik u sledećoj trudnoći. Analize se sprovode po strogo određenim protokolima, a rezultati se interpretiraju multidisciplinarnim pristupom, u kome učestvuju akušeri, genetičari, neonatolozi i patolozi.

Cljučne reči: fetalna autopsija, uzrok smrti, ispitivanje placente

Introduction

Pregnancy loss is one of the most common obstetrics complications affecting over 30% of conceptions. Most of them occur in the first trimester of gestation and are due essentially to problems with implantation or chromosomal anomalies and may not be clinically apparent.

However 12-15% of conceptions result in clinically recognized pregnancy loss. Fewer than 5% of pregnancies are lost after 10 weeks of gestation. The late fetal deaths are particularly devastating for families and clinicians. And answers to several questions are needed.

For the clinicians, what is the cause of the death? were complications of therapy? what is the recurrence risk? For the families, why did my baby die? Did I do something wrong? Will this happen again?

The autopsy of the fetus as well the placental examination can help by providing informations which can answer to some of these questions.

Aim of the Patologist

For a perinatal pathologist the main goal of the perinatal autopsy dissection is to characterize all pathologic findings (Figure 1) (1).

Fetal death is defined as death prior to the complete extraction or expulsion from its mother of a product of conception irrespective of the duration of pregnancy.

It is divided in early (<22 weeks of gestation), intermediate (between 22 and 27 weeks of gestation) and late (> 28 weeks of gestational age). Of these, early are designated as abortions whereas intermediate and late are known as stillbirths (2).

The key objectives of autopsy examination are identification of causes of death, elucidation of pathogenic mechanisms and quality control of clinical mechanism. Therefore a well-developed protocol must be followed and the results have to be interpreted by a multidisciplinary group including obstetricians, geneticists, neonatologists and the pathologist.



Figure 1: Well developed fetus in his amniotic cavity

Perinatal Autopsy Procedure

Before the autopsy, the pathologist must check the type of consent given, consult the clinicians, determine the questions that have to be answered and collect the informations about the pregnancy, gynecological history from the mother and fetal development (ultrasounds, laboratory tests, age of gestation and any data susceptible to help the interpretation of the autopsy findings).



Figure 2. Fetus with thanatophoric dysplasia. X-rays showing skeletal dysplasia (A) and External view of the same fetus (B)

It is important to receive a well preserved material (fetus and placenta). Then the external and internal examination must be performed after having obtained radiographs and photographs of the fetus and if necessary having proceeded to genetic analyses (3;4).

Photographs: External photographs of the perinate must be taken showing the full body features (antero-posterior and lateral) with close-ups of the face, hands, feets, external genitalia and any abnormalities found.

Radiographs: The main use of the X-rays is to assess primary ossification centers as a measure of fetal maturation, bone length as a measure of fetal growth and to detect bone abnormalities (Figure 2) (5; 6).

External examination: Measurements of crown heel, crown rump, head circumference, foot length and weight are taken for comparison with standard charts (7). A discrepancy of 20 mm indicates microcephaly or macrocephaly or a disproportionate body. Facial dysmorphism, inner and outer canthal distances are helpful.

For an appropriate examination of the fetus or infant a checklist is necessary. Some examples of findings will illustrates the importance of a well-followed protocol (8).

- **Head and skull:** Bulging fontanelles indicate, intracranial disorder. Defect of the scalp are seen in trisomy 13.
- **Skin:** Multiple hemangiomas suggest Osler-Rendu-Weber syndrome; leaf-shaped café-au-lait spots, a tuberous sclerosis. Meconium staining of the skin or orifices indicates intrauterine hypoxia.
- **Face:** Cataracts may be present in congenital infections as well as in systemic diseases, genetic or metabolism errors. Hypertelorism with short palpebral fissures, short nose, long smooth philtrum and thin upper lip are found in fetal alcohol syndrome. A proboscis with a cyclopic eye is frequent in trisomy 13. Choanal atresia, coloboma, heart disease, retarded growth and development are seen in CHARGE syndrome. Micrognathia or retrognathia are often seen in aneuploidy.
- **Neck:** Multiple ptérygium syndrome or postnuchal cystic hygroma occurs in monosomy XO, trisomy 21 and trisomy 18. A posterior midline swelling or defect could be due to a cervical meningocele (Figure 3) (9).



Figure 3: Cervical myelomeningocele

- **Chest:** A small abnormal shaped chest with short ribs is present in skeletal dysplasias (Figure 2).
- **Abdomen:** Abdomen distention can be due to ascites, organomegaly, intestinal obstruction or tumor.

- **Extremities:** Simian crease, sandal gap, typically occur in trisomy 21, polydactyly in trisomy 13 and some skeletal dysplasias. Overgrowth of a digit occurs in Proteus syndrome.
- **Genitalia:** External malformed or ambiguous genitalia can be associated with renal and anal anomalies.

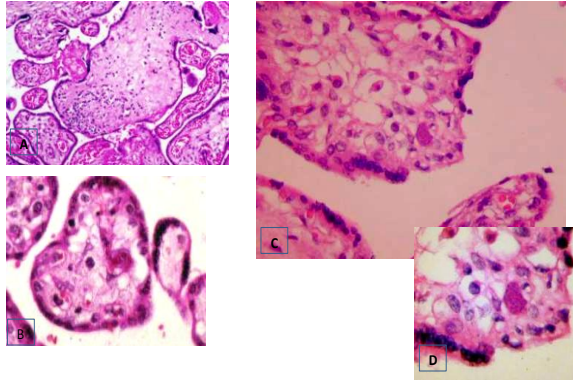


Figure 4. Placental infections:
· (A; B) viral inclusions of cytomegalovirus
· (C;D), toxoplasma cyst

Dissection

Standard neonatal textbooks explain in details the various dissection techniques. A systematic dissection of all internal organs must be conducted with care in order to visualize their locations and their interactions. A removal of the organs «en bloc» from the body cavity and separation of the organs in a second time remains the best technique to perform an optimal macroscopic examination. All the organs will be weighed and small samples of tissues will be submitted for histological analysis. Removal of the brain and the spinal cord will complete the dissection.

Placental Examination

Placental examination is required as an important part of the perinatal autopsy (10; 11). Findings of placental insufficiency (12) and fetal vascular obstruction/umbilical cord pathology are important findings in stillbirth related to cause of death (10) as well as the presence of placental infections (chorioamnionitis). In addition, placental examination in the midtrimester of pregnancy can also inform about a preterm delivery in previable fetuses (13).

A systematic analysis applies also to the placental examination. The umbilical cord, then the amniotic membranes, the fetal and maternal surfaces must be described and sampled. Hypercoiling of the umbilical cord indicates hypoxia. Chorioamnionitis is the most common placental lesion associated with cerebral palsy and preterm infants (14). Extensive placental infarction correlates with ischemic cerebral injury, particularly periventricular white matter necrosis in stillbirths.

Special Techniques

Special techniques may be required to make a definitive diagnosis such as cytogenetic analyses, fluorescent in situ hybridization for chromosomal abnormalities or PCR for detection of common and unusual infectious agents like *Toxoplasma gondii*, Rubella, Cytomegalovirus, Herpes simplex, Parvovirus B19 (15) or Coxsackie virus, *Trypanosoma cruzi*, *Treponema pallidum* (Figure 4) (16).

If a metabolic disorder is suspected, tissue samples need to be taken within 4-6 hours of death. Skin for fibroblasts culture should be placed in growth media at room temperature, muscle, heart, brain, liver should be frozen and taken for electron microscopy.

Conclusion

Fetal death remains a common, traumatic and in some cases preventable complication of pregnancy.

Common causes for fetal death include chromosomal abnormalities, genetic syndromes, infections, maternal diseases and abnormalities of multiple gestation.

Pathologic examination can confirm clinical diagnosis or provide definitive diagnosis.

Clinicians should encourage investigations of potential causes of fetal death to facilitate emotional closure and to assess recurrence risks.

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