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## Mandatory examinations to understand causes of stillbirth: the key role of autopsy and placental analysis

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### BACKGROUND

The interest about the phenomenon of Stillbirth (SB) significantly increased in the last 20 years with both Professionals and Health Authorities engaging in the organization of guidelines and recommendations. Meanwhile an Italian recommen-

dation will be available, most of the International Guidelines suggest, in order to reduce the rate of "unexplained stillbirth" (SB), a diagnostic strategy with a series of "principal investigations" (mandatory) and subsequently a series of "further investigations" (accessory) prescribed on the basis of the results of principal investigations [1-3].

“Principal investigations” are summarized in **Table 1**. Among them, foetal autopsy and a detailed macroscopic description of the placenta (chorionic disc, membranes and cord) as well as a histopathological examination of the placental tissue are mandatory. Thus, it is essential the collection of samples and their appropriate storage at the time of birth. Moreover, a medical record of the stillborn, including the report of the physical examination performed by an experienced perinatologist and the collection of relevant documentation, must always be provided to the pathologist before proceeding with the autopsy. It must be highlight that the stillborn diary has been included as a part of clinical documentation since 1999 [4].

## ISSUES TO BE ADDRESSED

Every-one of the above elements has a difficult implementation in clinical practice because of related

norms and laws, as well to their poor knowledge by perinatal professionals. Briefly, the main barriers are:

1. Definition of SB: the Italian rules require that the registration of a baby on Birth certificate (CeDAP) would be done every time a baby born [5]. However, in cases of stillborn it is common practice not to register a baby developed before 180 days (25+5 weeks) of gestation, as this corresponds to the definition of “abortion” according to ISTAT [6]. On the other hand, the WHO, according to medicine evolution as well as the actual ability of neonatal survival indicate that every case of intrauterine fetal death with a gestational age  $\geq$  22 weeks (or greater than 500 grams if gestational age is unknown) should be registered [7].
2. Administrative recognition: the stillborn lacks an administrative recognition since a specific Hospital Discharge Form (Scheda di Dimissione Ospedaliera or SDO, in Italy) for it does not exist. In practice, Professionals are using the name of the mother in their requests for autopsy and

**Table 1.** Principal investigations.

<b>At the time of diagnosis of stillbirth (Emergency Obstetric Room)</b>	
Begin stillborn medical record	Maternal and paternal anamnesis Past obstetric history Data collection on current pregnancy
Maternal exams	Blood sampling for foetal-maternal haemorrhage search (Cytofluorimetry Test) or alternatively Kleihauer-Betke test Count blood cells, coagulation, platelet count, glycosylated haemoglobin, TSH reflex Blood Group ABO and Coombs test (if not available) Anti-HIV 1-2, <i>Treponema pallidum</i> (screening), <i>Toxoplasma gondii</i> IgG and IgM (if not available) Serology for Herpes, CMV, Parvovirus B19, Enterovirus in case of clinical suspicion Varicella, Herpes Simplex 1-2, Measles, Mumps, Rubella (IgG and IgM); only in the case of suggestive signs of infection during pregnancy and in the absence of vaccination Virus Zika, Malaria Test: in case of clinical suspicion or exclusively in women from endemic areas Vagino-rectal swab for GBS
Amniocentesis	Microbiological culture (aerobic and anaerobic bacteria) Karyotype or QF-PCR
<b>At birth</b>	
Investigations on the stillborn	Physical examination (filling in the “neonatal part” of the stillbirth chart) Intracardiac Puncture: obtain as much blood as possible for the following samples: 1 ml for blood culture for the research of anaerobic bacteria (1 container) and mycetes and aerobic bacteria (1 container) (stored at room temperature) If blood remain, 1 ml for blood group ABO and Coombs Test (Stored at room temperature) Foetal oro-pharyngeal swabs (in depth): 1 sample for detection of aerobic bacteria and yeast 1 sample for detection of Mycoplasma and Ureaplasma Diagnostic and memory photographs Biopsy: if the karyotype is not already known, in the absence of placenta samples and at discretion of the neonatologist, a biopsy on the fascia lata (periumbilical or inguinal region) could be performed (collected in a sterile urine container containing medium for cytogenetic exam) Foetal autopsy
Placenta and Cord examination (by an expert in perinatal pathology)	Macroscopic examination (report infarcts, detachments, thrombosis of the umbilical cord, tight knots, etc.) Microbiological cultures: 2 placental deep swabs on both maternal and foetal surface (aerobic and anaerobic placenta cultures) Cytogenetic analysis: if the karyotype is not already known, 1 sample from a block for the cytogenetic investigation should be taken with the appropriate forms attached together with the signed parents' consent form (if requested according to national Legislation) Histopathological examination to be performed according to the Amsterdam Criteria. The phone number of the referent physician must be provided to the pathologist.

other exams (“child from...”), thus obliged to consider the child not as a separate entity, but still a portion of the mother’s body.

3. The apparent conflict existing between the so-called “SIDS-SIUD Law” (which provides for the consent of both parents for the application of the protocol for stillbirths and deaths occurring in the first year of life) [8], the indications provided by the Mortuary Police Regulation currently in force in Italy [9] and the aforementioned Prime Ministerial Decree of 9 July 1999 [10] (which provide for the obligation to perform an autopsy in all cases in which the cause of death is not clear and certifiable, under penalty of impossibility to proceed with the burial).

## PROPOSALS

In order to address the issues above reported, we suggest here some proposals:

- a. Waiting for national guidelines for post-mortem reports those produced by the Royal College of Pathologists could be used as a guide for reporting perinatal post-mortem examinations in case of SB [11-13]. The final report should be forwarded to the referring clinician.
- b. The placenta, after the macroscopic description by the clinicians, must always be kept refrigerated and promptly sent, without fixation, for histologic examination.
- c. To ensure the quality of histological exams, it is essential that each Birth Centre could be provided by an expert in feto-placental pathology. Otherwise, the transportation of placenta and SB to a centre with appropriate expertise should be arranged.
- d. Waiting for new and adequate rules, it is mandatory that each Birth Centre makes the performance of the required investigations on SB (body, fluids, tissues...) possible, even addressing “shortcomings” such as labelling SB investigation requests with mother’s name adding “child of”, in accordance with Regional Authorities. Moreover, clinicians should discuss the value of the autopsy with parents in every case of perinatal death. In order to obtain a valid and complete consent, discussion should include: the value of autopsy, the chance that some potential causes of death could be excluded, the possible implications for future pregnancies and, finally, the guarantees to care and respect of the body.

Finally, given the high value of the autopsy in the management of foetal death, it is mandatory that there are no interpretative confusions – on the relevant legislation, namely among professionals. The idea that the autopsy can and must always be performed has to be strongly emphasized, among clinicians and parents; they are solely requested to choice between two different applicative methods indeed: 1) instructions provided by the Decree of 2014 (requiring a specific double parental consent) [14]; 2) routine criteria of fetal-perinatal pathology (for which no consent is required since it is an investigation compulsory by law).

It is our hope that the advice reported in this brief paper clarify some points and support professionals in their effort to help families mourning a prenatal loss.

## COMPLIANCE WITH ETHICAL STANDARDS

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