OBSTETRICS

Evaluation of 1025 fetal deaths: proposed diagnostic workup

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OBJECTIVE: We sought to evaluate the contribution of different diagnostic tests for determining cause of fetal death. Our goal was to propose a workup guideline.

STUDY DESIGN: In a multicenter prospective cohort study from 2002 through 2008, for 1025 couples with fetal death ≥20 weeks' gestation, an extensive nonselective diagnostic workup was performed. A panel classified cause and determined contribution of diagnostics for allocating cause.

RESULTS: A Kleihauer-Betke, autopsy, placental examination, and cytogenetic analysis were abnormal in 11.9% (95% confidence interval [CI], 9.8–14.2), 51.5% (95% CI, 47.4–55.2), 89.2% (95% CI, 87.2–91.1), and 11.9% (95% CI, 8.7–15.7), respectively. The most valuable tests for determination of cause were placental examination (95.7%; 95% CI, 94.2–96.8), autopsy (72.6%; 95% CI, 69.2–75.9), and cytogenetic analysis (29.0%; 95% CI, 24.4–34.0).

CONCLUSION: Autopsy, placental examination, cytogenetic analysis, and testing for fetal maternal hemorrhage are basic tests for workup after fetal death. Based on the results of these tests or on specific clinical characteristics, further sequential testing is indicated.

Key words: antepartum stillbirth, cause of death, intrauterine fetal death, workup

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Fetal death is a devastating experience for parents and caregivers. A complex chain of events often precedes the fetal death. Health care workers are responsible for providing support to families and for investigating the cause of death. This information can give insight into why death occurred, which will aid parents in the mourning process. Furthermore, it will be of value in determining recurrence risk, counseling and prevention for future pregnancies, and audit of the care provided, and it enables comparison of health care.[1]

★ EDITORS' CHOICE ★

Unfortunately the cause of death is reported as unexplained in up to two thirds of stillbirths.[2,3] Using a systematic and well-defined approach to evaluate the cause of death reduces this percentage.[4] However, the optimal workup after fetal death has not yet been established and local protocols differ and are often extensive. Consequently, there is a debate on which tests and examinations should be included in an investigative workup to ensure an acceptable chance of determination of the cause of fetal death.

Several reviews on the workup after fetal death have been published,[3,5,6] however a prospective, systematic evaluation of a large cohort of fetal deaths has not yet been performed. Therefore we prospectively analyzed all diagnostic tests of an extensive protocol in which the contribution of each test was evaluated for determining the cause of fetal death according to the Tulip classification.[7] Our goal was to propose a guideline for an optimal workup after fetal death in terms of a high percentage of explained fetal deaths in combination with a minimum of testing.

Materials and Methods

In 2002, we initiated the prospective intrauterine fetal death (IUFD) cohort study in 50 Dutch secondary and tertiary referral hospitals. Inclusion criteria were singleton IUFD diagnosed antepartum ≥20 weeks' gestation. Pregnancy terminations and intrapartum deaths were excluded. The study was approved by the review boards of all hospitals and informed consent was obtained from all participants.

Diagnostic protocol

Data included medical and obstetric history and details on pregnancy and deliv-

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ery. Before the study started we examined local protocols of participating hospitals regarding diagnostics after IUFD. Subsequently the study protocol was based on these local protocols. Diagnostic tests were included in the study protocol if 70% of hospitals performed these tests after IUFD. For the study all participating hospitals followed the study protocol (Figure 1) and these tests were offered to all women with an IUFD so that each couple with IUFD was managed the same way.

Maternal and fetal blood test results were compared to local laboratory reference values and if greater, were considered abnormal. Maternal and fetal viral serology and microbiological cultures were positive if respectively immunoglobulin levels or culture colonies exceeded the reference values in the local laboratory.

Maternal plasma levels collected on induction of labor of antithrombin, protein C activity, total and free protein S antigen, and Von Willebrand factor (VWF) were measured and the thrombophilias factor V Leiden, prothrombin G20210A mutation (PTG20210A), and lupus anticoagulant were determined in the central laboratory.[8] Presence of maternal anticardiolipin antibodies and a random maternal plasma homocysteine (abnormal >18.5 μmol/L)[9] were tested in local laboratories.

Autopsy and placental examination were performed by surgical and perinatal pathologists in participating hospitals. We urged pathologists to follow the pathology study protocol based on the guidelines of the Royal College of Obstetricians and Gynecologists, the Royal College of Pathologists, and the College of American Pathologists.[7] Cytogenetic evaluation was performed in genetic centers[10] and radiography and magnetic resonance imaging (MRI) by local radiologists.

Adjudication of cause of death

After individual classification of the cause, mechanism, origin of mechanism, and determination of contributing factors of fetal death according to the Tulip classification[7] by an experienced multidisciplinary panel (consisting of 2 obstetricians, an obstetric resident, a perinatal pathologist and, if needed, expertise by a neonatologist, geneticist, or microbiologist), consensus was reached after discussion. The cause was defined as the initial, demonstrable pathophysiological entity initiating the chain of events that had irreversibly led to death. Contributing factors such as smoking and obesity were also identified. In addition, comorbidity was noted such as: hypertension-related disease during pregnancy including chronic hypertension, pregnancy-induced hypertension, preeclampsia, HELLP syndrome, and superimposed conditions.[11] Diabetes-related disease during pregnancy included types 1 and 2 diabetes mellitus and gestational diabetes with or without medication.[12]

Value of diagnostics

Contribution of each diagnostic test for determination of cause of death according to the Tulip classification was evaluated by the same multidisciplinary panel first individually and secondly during the panel sessions. Diagnostics were adjudicated valuable if "establishing cause of death" (an abnormal result of a diagnostic test established a cause) or "excluding cause of death" (a result excluded a cause of death when there was a suspected cause of death based on clinical findings or review of the medical history, current pregnancy, or antenatal investigations). We also registered if a test was "missing for determination of cause of death" (if there was a suspected cause, the test exploring that cause was missing).

Statistics

Categorical variables were expressed as counts and percentages, and continuous data as means with SD or median and ranges, with exact 95% confidence intervals (CIs) given when appropriate. Differences between groups were evaluated by the Fisher exact test or χ^2 test for categorical data. A 2-tailed P value $< .05$ was considered to indicate statistical significance. Statistical analyses were performed using software (SAS, version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

From 2002 through 2008 a total of 1164 couples and their fetal deaths were included, of which 1025 were studied (Figure 1). Investigation into inclusion rates by comparison of death registration yearbooks from participating hospitals yielded an average inclusion of 75% of all IUFDs eligible for the study. Reasons for not including IUFDs were: denied informed consent, a language barrier, logistic problems, and the doctor's reluctance to include women because of an already "known" cause of IUFD at birth. This involved deaths with placental abruption, known chromosomal abnormalities, and major congenital anomalies, which resulted in an underrepresentation of such deaths in our cohort.

Median age of mothers was 30 years (range, 17–51 years) and median gestational age at determination of IUFD was 32 weeks and 0 days (range, 20 weeks and 0 days–42 weeks and 4 days). The distribution of maternal ethnic origin was 87.1% Caucasian, 4.6% African, 3.8% Eastern, and 4.5% other. Of these mothers 52.7% were nulliparous. Median fetal weight was 1528 g (range, 12–5410 g). Of these babies 37.2% were small for gestational age (<10th growth percentile) and 10.1% large for gestational age (>90th growth percentile) according to Dutch Kloosterman[13] growth charts.

Diagnostic protocol

How often a test of the study protocol was performed varied from 98.7% for placental examination to 3.2% for expert external fetal examination (Figure 1). The results of various abnormal maternal blood tests and the number of women tested are presented in Table 1. Of the women with increased glycated hemoglobin (HbA1c) (7.9%), 61.8% were not known to have diabetes-related disease. Macrosomia and obesity, known risk factors for diabetes,[14] were more prevalent in this group compared to the group with normal HbA1c. Fetal blood tests derived from the umbilical cord were only performed in 10.5% mainly due to the impossibility of drawing (enough) blood after birth.

We recently published on the contribution of coagulation tests.[8] As shown in Table 1, in women with IUFD we more often observed decreased plasma levels of antithrombin (17.1%) and protein C