Intrauterine Fetal Demise

The value of a work up in the setting of a stillbirth after 20 weeks is for counseling for future pregnancies, possibly to reduce the risk of subsequent stillbirths, to decrease morbidity, to facilitate emotional closure for the woman and her family, (Silver 2010) and for humanitarian reasons so that, according to McPherson, families know that their child is valued. From a public health and scientific perspective, a systematic evaluation of the circumstances and associations with stillbirths may assist in investigations that could lead to preventive strategies.

When counseling patients in these circumstances, it is important to communicate that even with a complete evaluation, that some cases remain unexplained. The work up needs to consider both the potential cost and the potential for yield from the work up. A standard medical, surgical, psychological and obstetrical history is critical. Attached there is a recommended questionnaire to use as a template (Silver 2010) that is recommended for all cases.

There are some assessments in addition to the thorough history described that should be offered and hopefully included in assessments of all still births.

Assessments for all stillbirths

1. Description of the fetus and placenta by the delivering provider.
    a. Fetal and placental weight
    b. Foot length
    c. Gestational age
    d. Description of cord
        i. Position
        ii. Number of vessels
        iii. Any visible abnormalities
        iv. Insertion site on placenta (Central, marginal, velamentous)
        v. Any irregularities (compression, etc)
        vi. Length of cord
        vii. Degree of coiling
            a. Cord coiling: >0.3 coils/cm considered hypercoiled: seen in 37% of stillbirths. < 0.1/cm: decreased. 29% of stillbirths

    e. Placental description
        i. Adherent clot, membrane opacity, infarcts, other irregularities?
        ii. Meconium

    f. Fetus description
        i. Degree of maceration

ii. External description including face, limbs, spine, genitalia, patency of anus, palate. If dysmorphic features are noted, consider genetic consultation for formal dysmorphology exam.
iii. Gender assignment

2. Placental pathology
   a. Vasculature
   b. Evidence of infection
   c. Histology
   d. Abnormalities
   e. Evidence of hypoxia
   f. Multifetal placentation, vasculature

3. Autopsy
   a. Counseling: 26-51% of the time, an autopsy reveals important information with respect to counseling, future pregnancies (Silver, 2010)
   b. Looking specifically for evidence of infection, anemia, hypoxia, metabolic abnormalities, birth defects, estimate of time demise to delivery.
   c. Discuss history with pathologist
   d. If patient declines autopsy, request to have dysmorphologist examine fetus in the morgue; MRI post mortem; partial autopsy

4. Karyotype and microarray
   a. 8-13% of all stillbirths; 20% with IUGR or anomalies
   b. Amniocentesis much preferred to post-delivery tissue.
   c. 100% successful karyotype with amnio; 78% with tissue (Border 2009);
   d. Microarray yields results more often than karyotype analysis (Reddy, 2012). However, most stillbirths due to a genetic abnormality are still due to the most common aneuploidys (trisomy 18, 13, 21, monosomy X).
   e. Order 5 cell karyotype, if karyotype is normal and there is evidence of dysmorphic features and/or no obvious obstetric reason for IUFD (i.e. abruption), reflex to microarray (http://labs.unchealthcare.org/forms/cyto_req_inpt.pdf - see option for microarray with karyotype (5 cell analysis)). Microarray has a higher yield in providing a genetic diagnosis in fetuses with congenital anomalies and is especially valuable in these cases and in cases where karyotype results cannot be obtained.
      i. A genetic counselor can come and meet with the couple for an in-patient consultation if desired to review some of the issues unique to microarray including incidental findings of adult-onset or low penetrance conditions, variants of uncertain clinical significance, and inadvertent finding of consanguinity. Call 966-2229 if in-patient consultation is desired.

f. If tissue sample to be obtained, use placental block (1x1 cm) taken from below the cord insertion site on the unfixed placenta, an umbilical cord segment 1.5 cm in length and internal fetal tissue such as the costochondral junction or patella. Do not use skin. Obstetrician can and should obtain cord and placental tissue; pathologist should be asked to send deep fetal tissue at time of fetal processing.

5. Assessment for fetal-to-maternal hemorrhage
   a. 3-14% of all stillbirths
   b. Massive hemorrhage (>20% of blood volume)
   c. Recommend fetal bleed screen prior to induction; can be done up to 2-3 weeks post delivery.

6. Indirect Coombs (if not completed earlier in pregnancy)
   a. If not performed during this pregnancy
   b. Repeat only if fetus is hydropic.

7. Toxicology Screen
   a. Maternal serum or urine; fetal tissues such as meconium, hair or cord

8. Infectious work up
   a. Up to 20% in cases < 28 weeks.
   b. Parvo B 19: up to 8% of stillbirths based on viral nucleic acid in placenta
   c. Syphillis
   d. Without clinical or histologic evidence, TORCH infection w/u is of unproven utility.

9. Thrombophilia
   a. Lupus anticoagulant IgG and IgM
   b. Beta 2 Glycoprotein antibody
      i. 40 mpl/gpl or >99thth percentile considered positive (confirmatory study will be repeated at 12 weeks if positive)
         Low titers and Pos IgA isotype of uncertain significance
         Most likely if + preeclampsia and or PE
   c. Antiphospholipid antibodies
   d. Other thrombophiias if severe placental pathology, IUGR, history thrombosis
   e. Do not recommend Factor V leiden, prothrombin gene mutation, protein C and S, unless family history.
   f. Do not recommend MTHFR

10. Consideration in Some Stillbirths
    1. History of pruitutus: check bile acids, LFTs
    2. History of PPROM, cervical insufficiency, preterm labor or Malpresentation
        a. Consider uterine abnormalities
        b. Interval hysterosonography or MRI or HSG
    3. Glucose, thyroid testing
    4. Antithrombin III; Protein C and S 6 weeks
    5. Creatinine

11. Generally not useful
    1. ANA
    2. TORCH

12. Additional things to consider
    - Photos
    - Grief counseling
    - Social work
    - Pastoral care
    - Follow up

TABLE 1. Essential Components of History

- Details of the current pregnancy
  - Maternal age
  - Gestational age (supportive evidence including sonograms)
  - Medical conditions complicating pregnancy
    - Pregnancy-induced hypertension
    - Gestational diabetes
    - Cholestasis of pregnancy
    - Viral illness
  - Multifetal gestation
  - Known pregnancy complications
    - Preterm labor
    - Rupture of membranes
    - Fetal structural or chromosomal abnormalities including abnormal serum screening
    - Infections
    - Trauma
    - Abruption
  - Maternal symptoms suggestive of above complications
  - Maternal serum marker screen
- Maternal medical history
  - Chronic illnesses
    - Diabetes
    - Thyroid disease
    - Autoimmune disease
    - Hypertension
    - Cardiopulmonary disease
  - History of pertinent acute conditions
    - Prior venous thromboembolism
  - Substance use
  - Known genetic abnormalities
    - Balanced translocations
    - Single gene mutations
- Pregnancy history
  - Recurrent miscarriages
  - Previous stillbirth or neonatal demise
  - Previous pregnancy complicated by
    - Growth restriction
    - Hypertension
    - Fetal anomalies
    - Abruption
- Family history
  - Developmental delay or mental retardation
  - Stillbirth or recurrent miscarriage
  - Genetic syndromes
  - Significant medical illnesses (pulmonary embolism and severe hypertension)

All Stillbirths

1. Complete History (see example)
2. Description of fetus, cord and placenta by delivering provider
3. Encourage autopsy
    a. If declines, consider MRI
4. Karyotype
    a. Amnio preferred or placental biopsy; tissue sample if declines with reflex to microarray
5. Flow cytometry for fetal to maternal hemorrhage
6. Indirect coombs if not completed earlier in pregnancy and fetus not hydropic
7. Maternal toxicology screen
8. Parvovirus IgG and IgM; Syphills screen
9. No other infection work up without clinical or histologic evidence
10. Lupus anticoagulant (IgG and IgM)
11. Beta 2 Glycoprotein antibody
12. HIV if not done prenatally

Consider for some stillbirths

1. If severe placental pathology, IUGR, history of thrombosis, family history of thrombosis/emboli then consider Factor V Leiden, Prothrombin gene mutation, Protein C and S (at 6 weeks); Antithrombin III.
2. History of pruritus: Bile acids, LFTS
3. History of PPROM, cervical insufficiency or malpresenation, consider interval hydrosonography, MRI or HSG
4. Glucose (If LGA), Hgb A1C, Thyroid testing
5. Creatinine
6. If the fetus is dysmorphic or IUGR, even if the patient declines an autopsy, request a genetic consult and alert them that there is a fetus to be examined in the morgue.

Unlikely to be helpful

1. ANA
2. TORCH titers

In L&D, use the pre-packaged amniocentesis tray and cytogentic request from. Obtain at least 3 tubes of fluid (Label them to indicate which tube is #1, #2 and #3)Provide as much data as possible, including a description of the fetus. Package the tubes with the paper work and label the transport bag "For cytogentics". Leave a message on the cyto lab's answering machine (6-1595) indicating the name of the patient, indication of testing, and contact information. If amnio or placental biopsy is declined

Tissue sample
*Placental block 1x1cm under the cord insertion; umbilical cord segment 1.5 cm long; internal fetal tissue sample like costochondral junction or patella; do not use skin.

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This protocol is designed to assist the primary care provider in the clinical management of a variety of problems that occur during pregnancy. They should not be interpreted as a standard of care, but instead represent guidelines for management. Variation in practices should take into account such factors as characteristics of the individual patient, health resources, and regional experience with diagnostic and therapeutic modalities.

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