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

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

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

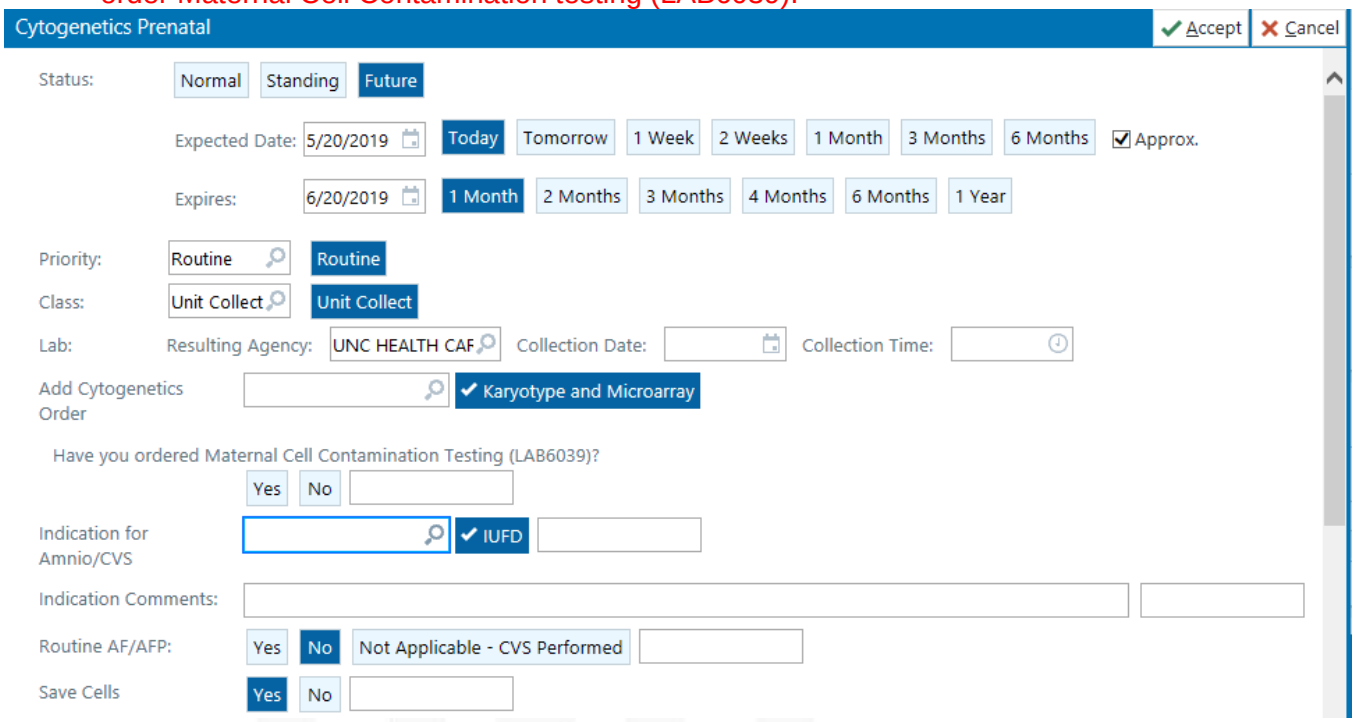
3. Autopsy
   a. Counseling: 26-51% of the time, an autopsy reveals important information with respect to counseling, future pregnancies (Silver, 2010)
   b. There is **no cost** for an autopsy when a patient has had care at UNC Hospital (https://www.uncmedicalcenter.org/mclendon-clinical-laboratories/directory/autopsy-service/)
   c. Looking specifically for evidence of infection, anemia, hypoxia, metabolic abnormalities, birth defects, estimate of time demise to delivery.
   d. Discuss history with pathologist
   e. If patient declines autopsy, request to have dysmorphologist examine fetus in the morgue; MRI post mortem; partial autopsy
   f. MRI for stillborn fetus
      i. Order the MRI (IMG5834)
      ii. Let the patient's nurse know that the MRI needs to happen BEFORE the fetus is taken to any other location
      iii. Request that the nurse call MRI and arrange for transport to pick-up the fetus then return it to L&D.

      *Ideally, the MRI should be done before leaving L&D

4. Karyotype and microarray
   a. 8-13% of all stillbirths; 20% with IUGR or anomalies
   b. Amniocentesis much preferred to post-delivery tissue. Cytogenetic success rates were significantly higher for invasive testing pre-delivery (85%) than for postpartum tissue analysis (28%, P<.001) [Korteweg FJ , 2008, Obstetrics and Gynecology]
   c. 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 aneuploidies (trisomy 18, 13, 21, monosomy X) **we therefore recommend karyotype (20 cell) with reflex to microarray.**
   d. Pre-test counseling points to consider: microarray costs more, microarray can result in variants of uncertain significance, can reveal low penetrance, adult onset conditions, consanguinity, microarray cannot detect mechanism of aneuploidy (non-disjunction vs. Robertsonian translocation).
   e. A genetic counseling appointment can be made post-delivery preferably at least 6 weeks after loss to discuss results of cytogenetic testing sent in cases of stillbirth.

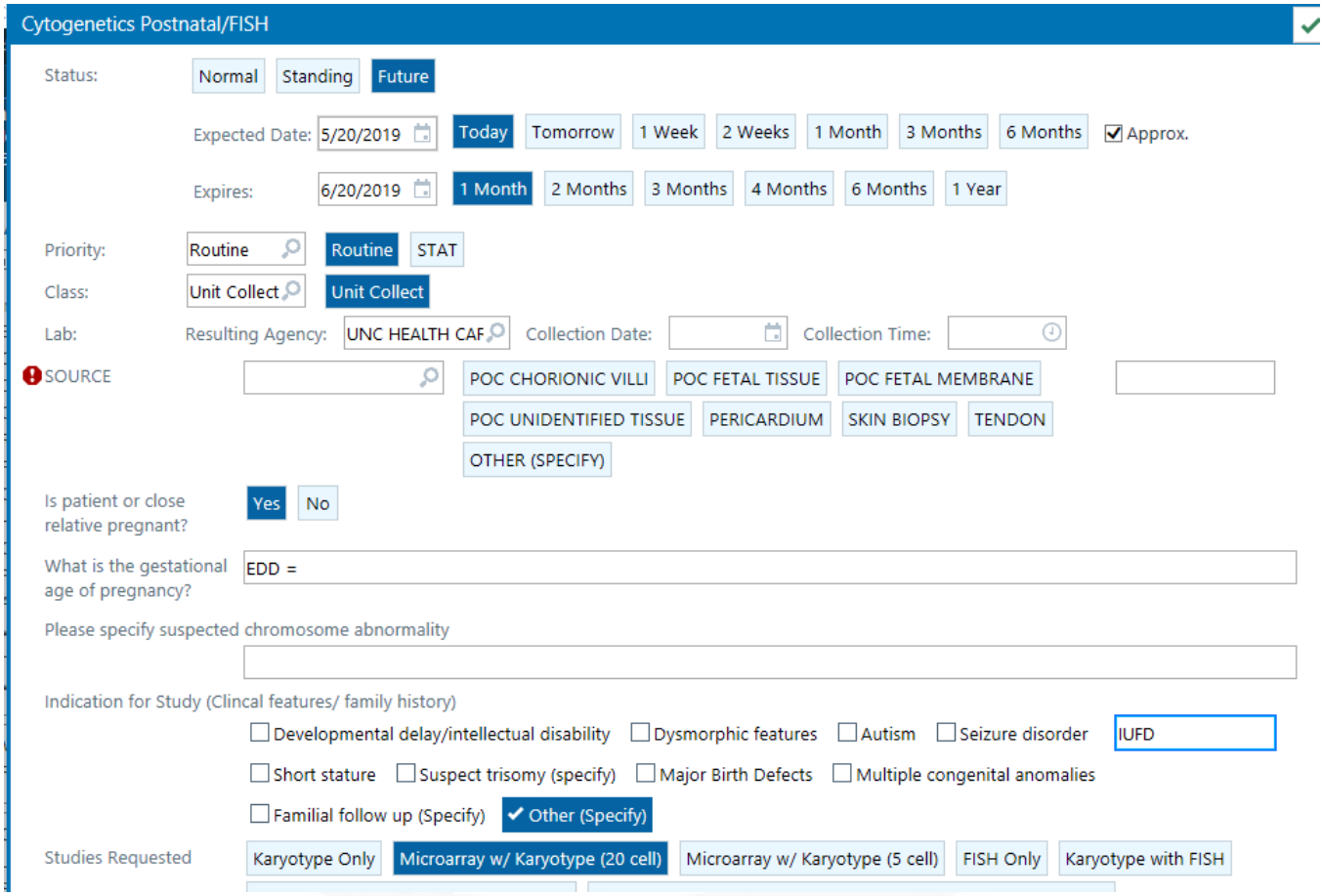
Place ambulatory referral to reproductive genetics in EPIC if desired.

f. **First tier sample**: Amniocentesis (EPIC order LAB5501): Obtain 30mL of amniotic fluid (90 mL if procedure is due to polyhydramnios). Place "Cytogenetics Prenatal/FISH" order (LAB5501). Default to "Unit collect", "Save cells" if additional genetic testing may be indicated. Click on what testing is desired in "add Cytogenetics Order". If ordering microarray in fetus that is female or of unknown sex you must also order Maternal Cell Contamination testing (LAB6039).



g. **Second tier samples:** Products of conception: Obstetrician should offer to send post-delivery tissue if invasive testing was declined/not performed pre-delivery. It is optimal to send as **many sources of tissue** as possible if an amniocentesis was not performed.
   i. First tier tissues: Placenta
      1. Collect several ~10 mm pieces of the chorion containing villi in **thawed** culture medium
   ii. Second tier tissues: Cord blood or umbilical cord tissue
      1. Blood from umbilical cord: Ideally, 3 mL should be placed in a Sodium heparinized tube (green top).
      2. 2-3 cm umbilical cord in **thawed** culture medium
   ii. If autopsy requested: Deep fetal tissue can be sent
      1. Deep fetal tissue: Pathology requisition should request deep fetal tissue at time of fetal processing during autopsy.
      2. This often has the lowest yield depending on time since demise occurred

Products of conception (LAB5505): Obtain a cytogenetics specimen collection medium (pink) from freezer on L&D or Core Lab. Place several ~10 mm pieces of the chorion containing villi in the tube of **thawed** culture medium. Can also place 2-3 cm umbilical cord in a second container of thawed culture medium. Submerge the tissue completely in the medium. DO NOT PLACE SAMPLE IN FORMALIN, PLACE IN UNTHAWED MEDIA, OR SEND IN SALINE since viable cells are needed for karyotyping. Send specimen with orders (Cytogenetics Postnatal/FISH) immediately to Core Lab. Do not freeze. Do not refrigerate. If ordering microarray in fetus that is female or of unknown sex you must also order Maternal Cell Contamination testing (LAB6039).



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 thrombophias 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. For losses >20 weeks recommend karyotype (20 cell) with reflex to microarray
    a. Amnio preferred specimen after 15 weeks; fetal deep tissue sample preferred sample if declines amniocentesis; placenta last resort
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; Syphilis 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. Obtain at least 30 mL 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 and label the transport bag “For cytogenetics”. Leave a message on the cyto lab’s answering machine (6-1595) indicating the name of the patient, indication of testing, and contact information.

Tissue sample
Place several ~10 mm pieces of the chorion containing villi and/or 2-3 cm of umbilical cord in the tube of **thawed** culture medium; If autopsy accepted, pathology can also send deep fetal tissue (such as paricardium or Achilles).

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