Identifying Problem Pregnancies in the Developing World

Over the past two centuries there have been enormous improvements in the incidence of perinatal morbidity and mortality (i.e., infant illness and death in the weeks just prior to and just after birth). Many of these gains have been attributed to the increase in adequate prenatal care that women receive during pregnancy. A major focus of that care is in the prevention of early delivery and low birthweight of babies: In one classification of United States data in a 2005 report, medical problems attributable to short gestation and low birthweight are the second leading cause of infant mortality (after congenital malformations).

As might be expected, perinatal mortality remains a large problem in much of the developing world where adequate prenatal care is not as available: In the 2005 report from the World Health Organization it was noted that 1 in 5 African women lose a baby during their lifetime, as opposed to the 1 in 125 rate in richer countries.
In less developed countries, many urban pregnant women receive their only care from nurses in busy antenatal community clinics, where they will typically also deliver their babies. A challenge in this environment is to develop low technology methods of identifying problem pregnancies so that these can be appropriately referred to a higher level of care in a timely manner. Some problem outcomes of concern are low birth weight babies (<2500 gms) as might be caused by either pre-term delivery (prior to the 38^{th} week of gestation) or small for gestational age (SGA) babies (below the 10th percentile of birth weight for the gestational age at which they are born).

Normal Pregnancy

Pregnancy is defined as period between the time a fertilized egg is implanted in the uterus until the time of delivery (or in some cases, fetal resorption). In humans, successful implantation occurs 7-14 days following fertilization, though many fertilized eggs do not develop appropriately and/or never implant. In an uncomplicated pregnancy, delivery occurs approximately 38 weeks after fertilization.

Fertilization of an egg typically occurs very soon after ovulation, but as the exact timing of ovulation is not readily observable in most cases, we typically measure length of gestation from the date of the woman's last menstrual period (LMP). In women who have regular 28 day menstrual cycles, ovulation occurs approximately two weeks after the LMP, hence the "typical" live delivery is at a gestational age of 40 weeks.

The period of gestation is typically divided into three "trimesters" of approximately equal length. During the first trimester, the fertilized egg divides and begins embryonic development. The embryo implants in the uterus and develops a placenta through which nutrients and wastes are exchanged between the embryo/fetus and the mother throughout the pregnancy. During the embryonic phase (up to approximately 10 weeks after the LMP), the organ systems develop through cellular differentiation. Following this period, the developing baby is referred to as a fetus. Development and growth continues through the second trimester, but the greatest weight gain of both the mother and the fetus occurs in the third trimester, which is typically regarded as weeks 27 to 40 of gestation.

It should be noted, however, that there is wide variation in length of menstrual cycles, timing of ovulation, and time from fertilization to delivery, and this leads to some imprecision in the estimation of "gestational age by dates" (i.e., the time from LMP). It is now standard obstetric practice in more developed countries to also estimate gestational age by making measurements of fetal size using ultrasound. Starting at around 13 weeks gestation, ultrasound measurements of crown-rump length, biparietal diameter (width of the cranium), and length of the femur are used to provide reasonably well calibrated estimates of gestational age. These measurements are thought to be most reliable as estimates of gestational age when they are made relatively early during the second trimester. Later in the pregnancy, trends in those ultrasound measurements (along with fetal abdominal circumference) are more used to assess whether the fetus is growing appropriately.

Common Complications of Pregnancy

There are a wide variety of maternal and fetal conditions that can lead to complications of pregnancy. Of particular interest for this study are the complications that relate to

- *Low birth weight (LBW):* Babies whose weights are below 2500 g at birth are at increased risk for disease and failure to thrive.
- *Pre-term delivery:* Babies born prior to 37 weeks of gestation will suffer from both low birth weight and inadequately developed organ systems. The respiratory system in particular is only fully developed late in pregnancy. Thus pre-term delivery is associated with many respiratory complications. (With the advent of modern medicine and neonatal intensive care, however, babies born as early as 23 weeks are now sometimes surviving, though there often do remain substantial long term medical problems with such pre-term deliveries.)
- *Small for gestational age (SGA):* Intra-uterine growth restriction (IUGR) may lead to babies whose size or weight is below the tenth percentile for their gestational age. This is often believed to be due to insufficient nutrition received by the fetus.

Maternal factors leading to these conditions include:

- Chronic medical conditions including diabetes and hypertension can greatly affect the course of pregnancy.
    - In diabetes, it is believed that the high maternal glucose levels cross the placenta and, in the presence of typically normal levels of insulin in the fetus, allow higher than average growth of the fetus. Babies of diabetic mothers are thus often “large for gestational age”. It should be noted that some women develop “gestational diabetes” that is not manifest except during pregnancy.
    - In hypertension, the blood supply to the uterus is sometimes insufficient to allow usual fetal growth.
- Acute medical conditions such as infection.
- Maternal response to pregnancy, such as pre-eclampsia. In pre-eclampsia, women develop high blood pressure, retain fluids (hence having rapid weight gain), and potentially progress to eclampsia involving generalized seizures, loss of pregnancy, and maternal death. One hypothesis for the cause of pre-eclampsia is some sort of decreased blood flow to the placenta (for instance, uterine artery constriction or blockage) that causes hormonal release leading to the hypertension. In the presence of pre-eclampsia, fetal growth is often restricted.
- Poor maternal nutrition that restricts availability of nutrients to the fetus.
- Maternal smoking that is associated with restricted fetal growth, perhaps in part through smoking’s effect on maternal circulation.
- Maternal factors leading to an inability to carry a pregnancy to full term, including an incompetent cervix or uterine anomalies leading to problems with the placenta or carrying the fetus.
- Multiple gestations. Twins, triplets, etc. may decrease the nutrients available for each fetus, as well as cause early delivery owing to the greater stress on the uterus/cervix.
- Genetic factors that affect the maternal ability to bear pregnancy.

Fetal factors leading to these conditions include:

- Placental insufficiency in which the interface between the uterus and the placenta does not allow adequate exchange of nutrients and oxygen. (Such problems could also be maternal in origin.)
- Genetic factors / abnormalities.

Typical Prenatal Care

Prenatal (antenatal) care typically involves regular monitoring of the pregnant woman to look for symptoms or signs indicative of various complications. Clinic visits are usually monthly during the first two trimesters, with increasing frequency later in the pregnancy. Items that are of particular interest include:

- Maternal blood pressure, which is used to screen for pre-eclampsia and other conditions that might affect the ability of the fetus to obtain proper nutrition and oxygen.
- Maternal weight, which is used to ensure that
    - the mother's nutritional status can provide for the developing fetus,
    - the fetus is growing, and
    - the mother's weight gain is not so great as to suggest excessive retention of fluids (a sign of pre-eclampsia- very rapid weight gain in a week is typically a sign of fluid retention rather than just excessive caloric intake).
- Fetal size. This is typically measured by the distance from the symphysis of the pelvic bones to the top of the uterus: the symphysis-fundal height (SFH).
    - SFH is typically useful starting at about 20 weeks of gestation, after which it tends to be approximately linearly increasing over time (with a very rough rule of thumb that SFH is approximately equal to weeks of gestation).
    - Measurement of SFH can be more difficult in extremely obese women in that the exact correspondence between SFH and gestational age is affected. Changes in SFH still generally tend to correlate well with change in fetal size.
    - SFH can be increased in certain conditions in which the volume of amniotic fluid is abnormally high. Hence, in those situations it may not be as indicative of fetal size.
    - After 36 weeks gestation (approximately) the fetal head engages into the pelvis (the "baby drops"), and that may cause a decrease in the SFH.

Research Questions

These data come from a cohort study in a peri-urban setting in the Western Cape, South Africa. 755 pregnant women with singleton pregnancies who could not afford private healthcare were followed from enrollment (on average at 22 weeks gestation) to delivery. At enrollment and at each subsequent clinic visit, each woman's weight and symphysis fundal height (SFH) were recorded. Symphysis fundal height is measured on pregnant women with a tape measure as the distance from the lowest to the highest part of their uterus. Both weight and SFH would be expected to increase over pregnancy. In addition, other characteristics of the mother were recorded, including parity and smoking status. At delivery, the sex of the baby, the baby's birth weight and the gestational age (week) of delivery were determined.

1. Is there evidence that weight profiles and/or SFH profiles over pregnancy differ between women who do and do not deliver pre-term, LBW, and SGA babies? Of greatest interest would be the association between measurements made between 20 – 30 weeks EGA and the three adverse pregnancy outcomes, in order to be able to refer high-risk women to more intense prenatal care.

2. Is it possible, using measurements taken prior to week 30 of pregnancy, to develop a model which accurately distinguishes between women who will and will not have growth retarded babies?

Available data

There are two data sets:

pregout.txt

This contains one record per woman

- mcode= mother's study ID
- ht=mother's height in cm
- age=mother's age at enrollment in years
- sga : small for gestational age 0=no, 1=yes
- parity=number of prior deliveries
- smoker: 1=yes, 2=no
- bweight=birthweight of infant in gms
- sex of infant: 1=boy, 2=girl
- gesage =gestational age at delivery (weeks)

preglong.txt

This contains one record for each clinic visit

- mcode= mother's study ID
- wk=gestational age of record (weeks)
- wt= mother's weight (kg) at that gestational age
- sfh= symphysis fundal height (cm) at that gestational age