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What we have learned about the design of randomized trials in pregnancy

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ABSTRACT

For nearly 30 years the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal–Fetal Medicine Units (MFMU) Network has been conducting randomized trials in pregnant women, many of which have changed clinical practice. Since 1986, the MFMU Network has conducted 29 randomized trials, of which the 17 trials started or completed since 2003 are described here. Study design choices are described including decisions regarding the fundamental questions to be answered and the rationale behind choices of primary and secondary outcomes. Some of the potential pitfalls, particularly relating to bias, that can affect the interpretation of trial results are described along with the mechanisms that the Network has used to avoid or minimize them.

Background

In the early days of randomized trials, women, let alone pregnant women, were rarely included. For medical conditions that affected women as well as men it was assumed that the treatment effect of a medication would be similar in women to those in men. As false an assumption as this might have been, it was even more unlikely to apply to pregnant women whose physiological state is quite different from non-pregnant women.[1] At the same time, the traditional reluctance to include pregnant women in randomized trials out of concern for maternal and fetal safety led to use of interventions and medications with unknown risk and the paradoxical situation of exposing more maternal–fetal dyads to potentially harmful interventions than if they had been enrolled in randomized trials. In his essay "Discovering the need for randomized controlled trials in obstetrics: a personal odyssey," Grimes describes how clinical interventions based only upon opinion or dogma, without solid evidence of benefit, permeated the practice of obstetrics.[2] The use of tocolysis and electronic fetal heart rate monitoring could be considered as examples. In 1979, Cochrane, the British epidemiologist and early champion of randomized trials, ranked the various medical specialties by the extent to which practices were based on valid evidence of effectiveness. Obstetrics was ranked easily in last place. Not only were randomized trials lacking for obstetrical interventions and management, but the strategies to treat pregnant women with pre-existing diseases were also lacking.[3]

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In the past 40 years there has been a "sea change" in regulations regarding inclusion of women in trials, including the establishment of the Office of Research for Women's Health. Partly as a result of Cochrane's observation, the urgent need for randomized trials specifically in obstetrics and maternal–fetal medicine and large enough to give reliable answers, was recognized.[4] In 1986, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) created the MFMU Network.[5] The goal of the Network is to provide the rationale for evidence-based obstetric practice with priority given to randomized trials. Similar initiatives were started in the UK and Canada. To date, the Network has worked on 29 randomized trials: 25 completed, three currently recruiting, and one in the process of implementation. In 2003, this journal published an issue on highlights from the MFMU Network, including lessons learned from the experience of conducting the first 12 trials.[6] In this article we describe some of the study design challenges particularly relevant to trials in pregnancy that we have faced in the next 17 randomized trials and how we have attempted to overcome them.

Choice of primary and secondary outcomes

For any randomized trial, a primary outcome should be specified (or more than one, as long as the statistical effect of multiplicity is adequately addressed). A good primary outcome is one that is clinically relevant and compelling, sensitive (i.e., likely to be responsive to the intervention), measured precisely and reliably, and measurable in all participants. Choosing a primary outcome for randomized trials in pregnancy can be complicated by the fact that the intervention to be evaluated is administered to one individual —the mother—but is frequently intended to benefit the other (s)—the fetus or fetuses. The balance of safety and effectiveness between the mother and the baby creates a challenge.

Of the 17 trials since 2003, 12 (trials 1, 2, 6–12, 14, 16, 17 in Table 1) were focused primarily on the fetus or infant. In each case, the intervention is at best inconvenient and at worst risky for the women. However, the primary question of the trial is really about the baby. Six of the 12 trials (trials 6–8, 11, 16, 17 in Table 1) were of interventions initiated in the second trimester to prevent preterm birth in high risk women. For all of these trials, the MFMU Network has chosen an endpoint based on preterm birth before a specific gestational age cutoff. In contrast, some study groups have used neonatal morbidity or mortality as the primary outcome, almost always as a composite. Their argument is that preterm birth is a surrogate for the morbidity and mortality experienced by a premature infant.[7] But it could also be argued that neonatal outcome is a surrogate for adverse health or disability after neonatal discharge. Therefore, using a pre-term birth cutoff as the primary outcome is logical since the very structure of the intervention, such as a pessary, is to prevent preterm birth from happening. If a trial is positive, however, it is possible that fetuses will be exposed to a new intervention as standard of care, so then conducting a long term follow-up of the children would be important.

It is important, to pick an appropriate gestational age cutoff for the population being studied—we have chosen 35 weeks for twin gestation and 37 weeks for singleton gestation. It should be noted that in all of these trials, fetal demise occurring before the cutoff is also included in the outcome. We found that this needed to be specified especially clearly in the case of multifetal gestation, as it is possible for example, to have a fetal loss in one twin while the other twin survives and may be born days or even weeks later. Of note, preterm birth not only satisfies all of the criteria for a good primary outcome, but it is probably the easiest of all outcomes to obtain. All that is needed is a standardized estimate of gestational age from a pre-randomization ultrasound and the delivery date.

Three of the trials (1, 2, 12 in Table 1) are of interventions intended to ameliorate the effects of premature birth in the baby when preterm delivery appears to be imminent. In the BEARS trial[8] (2 in Table 1) of repeated versus single dose corticosteroids, the primary outcome was a composite of neonatal morbidities including respiratory outcomes that are common in very premature babies and had been shown to be responsive to a single course of antenatal steroids. Of note, there was considerable discussion as to whether a safety secondary outcome should be elevated to the status of "primary" since there were growing concerns regarding the effect of repeated steroids on fetal growth.[9] Ultimately it was decided that a single efficacy endpoint was most appropriate, as that was the main question to be answered. However, we included neonatal anthropometric measures obtained with standardized equipment by trained research staff as major secondary outcomes in the protocol. We also conducted a follow-up study of the children at age 2–3 years, which included anthropometry.[10]

In the ALPS trial (trial 12 in Table 1) of corticosteroids for women at high risk of delivering in the late preterm period, the primary outcome was a composite endpoint describing the need for respiratory support in the first three days of life.[11] Follow-up of these children at 6 years of age is planned.

In each of the three trials in this group, the relatively complex primary outcomes required neonatal, neurodevelopmental or pediatric expertise beyond that of the MFMU trialists for outcome determination, which usually takes the form of a blinded review of the neonatal chart or standardized examination of the infant. The need for a multidisciplinary approach is a common characteristic of MFMU Network trials and other pregnancy trials where the main focus is the baby rather than the mother.

Three trials (trials 9, 10, 14 in Table 1) involved screening for and treating a maternal medical condition that could potentially have adverse consequences for the infant, but otherwise the mother would not normally need treatment. For one of these, the CMV trial (14), there was a discussion regarding the appropriate choice of primary outcome. The purpose of this ongoing trial is to evaluate monthly infusions of hyperimmune globulin versus placebo as an intervention for pregnant women who have been exposed to the cytomegalovirus (CMV) during pregnancy. Fetuses exposed to CMV in utero that acquire the infection are at high risk for death, hearing loss, chorioretinitis, neurodevelopmental delay, and other adverse outcomes as children, especially if