

**Limiting Systematic Reviews to RCTs
Can Impose Profound Bias:
The Case of Cesarean versus Vaginal Birth**

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13th Cochrane Colloquium
Melbourne, Australia
October 25, 2005

Intertwining Dilemmas of Restricting Evidence to RCTs

- Methodologic (e.g., power; crossover after randomization)
- Logistic (e.g., adequate funding; follow-up)
- Cultural (e.g., orientation of clinicians)
- Ethical (e.g., cannot wait for long-term knowledge; equipoise?)



Maternity Center Association

- National non-profit advocacy organization
- Established 1918
- Promotes welfare of mothers and babies with no conflicts of interest
- Long-term national program to promote evidence-base maternity care, 1999-



Review Context

- 4 million mothers and babies annually, most healthy
- Rising record-level national cesarean rate
- Increasingly casual use of surgical birth
- Declining access to vaginal birth after cesarean (VBAC)

⇒ Important to understand harms associated with mode of delivery



Outcomes of Interest

- Foster informed decision making by seeking full accounting of harms that are meaningful and of potential interest to women
- Exclude surrogate markers: not meaningful to women, difficult to interpret
- Available systematic reviews had focused on incomplete set of adverse effects



What do women want to know?

U.K. and Australian postpartum surveys

- “necessary to know *every* complication of an epidural before having one”: 1/2
- “necessary to *most* complications ...” over 1/3
- “necessary to know *some* complications ...”: 7% and 15%, respectively

Bethune et al., *Int J Obstet Anesth* 2004

Yentis, personal communication



Review Results

Unless there is a clear, compelling and well-supported justification for cesarean section or assisted vaginal birth, a spontaneous vaginal birth minimizing use of interventions that may be injurious to mothers and babies is the safest way for women to give birth and babies to be born.

- Manuscripts in process
- Bibliography, evidence tables, consumer resources available at www.maternitywise.org/cesareanbooklet/



Follow-up Dilemma: Long-term Outcomes in Mothers

Can we anticipate good RCT measurement of:

- chronic pelvic pain
- bowel obstruction
- infertility – involuntary
- infertility – voluntary
- ectopic pregnancy/cesarean scar pregnancy

All were worse in women with previous cesarean



Follow-up Dilemma: Long-term Outcomes in Mothers (cont)

Can we anticipate good RCT measurement of:

- placenta previa
- placenta accreta
- placental abruption
- uterine rupture
- maternal death

All were worse in women with previous cesarean



Follow-up Dilemma: Long-term Outcomes in Babies in Future Pregnancies

Can we anticipate good RCT measurement of:

- stillbirth and early neonatal death
- low birthweight and preterm birth
- malformations
- central nervous system injury

All were worse in babies that developed in a cesarean-scarred uterus



Follow-up Dilemma: Long-term Outcome in Babies after Present Pregnancy

Can we anticipate good RCT measurement of:

- asthma, in childhood and adulthood

Was worse in babies born by cesarean section



Follow-up Dilemma: Intermediate Outcomes in Mothers

Can we anticipate good RCT measurement of:

- rehospitalization
- more severe and longer-lasting pain
- self-esteem
- overall mental health
- overall functioning
- psychological trauma (unplanned cesarean only)
- depression ??

All were worse in mothers with cesarean section



Power Dilemma 1: Less Frequent Outcomes in Mothers

In addition to many less frequent outcomes already noted, can we anticipate good RCT measurement of:

- surgical injury
- emergency hysterectomy
- blood clots and stroke
- death (associated with surgery/anesthesia rather than underlying condition)

All were worse in mothers with cesarean section



Power Dilemma 1: Less Frequent Outcomes in Babies

In addition to some outcomes already noted,
can we anticipate good RCT measurement of:

- mild to severe respiratory problems
- surgical injury

Both were worse in babies born by cesarean section



Power Dilemma 1: Pool to Measure Less Frequent Outcomes?

Analysis of 1727 Reviews in *CDSR* 2003, Issue 3:

- enough participants for 1 or more adverse effects that might occur in 1%: 1% of all reviews
- among those reviews, most did not detect difference

Papanikolaou and Ioannidis, *Am J Med* 2004



Power Dilemma 2: Protocol Violation

- high level of protocol violation in many pregnancy and childbirth trials
- anticipate about 30% of women randomized to vaginal birth arm would have cesarean
- dramatically increases numbers needed to detect true differences



Dilemma of Co-Interventions

Can we anticipate good RCT measurement of:

- any urinary incontinence in mothers
- any anal incontinence in mothers
- brachial plexus injury in babies

All were worse with vaginal birth



Dilemma of Co-interventions (cont)

Cesarean vs vaginal birth RCT would capture effects of vaginal birth management practices:

- midline episiotomy
- instrumental delivery
- forceful, staff-directed pushing (vs reflex)
- pushing/giving birth in supine or lithotomy position
- fundal pressure
- perineal pressure

All have been associated with adverse effects in mothers

Many women experience several with vaginal birth

Best evidence does not support liberal or routine use



Dilemma of Pelvic Floor Management Standards

Current urogynecology standards make interpretation difficult:

- Largely studied during recovery period; need longer follow-up
- Cannot interpret surrogate markers
- Inclusive definitions without reference to meaning to women



No Serious Dilemmas

Straightforward to measure with RCTs:

- infection
- length of hospitalization
- women's ratings of birth experience
- amount of early mother-baby contact
- women's initial reactions to their babies
- establishment of breastfeeding
- perineal/vaginal pain

First five favored vaginal birth; last favored cesarean



Calls for Elective Cesarean RCT

“It will require a randomized, controlled, prospective study to clearly define the benefits of elective prophylactic cesarean delivery versus trial of labor. As the evidence suggesting superior outcomes from elective prophylactic cesarean delivery continues to mount, the time has come for a controlled multicenter clinical trial to deny or confirm the benefit of elective prophylactic cesarean delivery.”

Hale and Harer, *ACOG Clinical Review* 2005 editorial



Equipoise?

Does this meet equipoise test for RCT of vaginal birth vs elective cesarean?

Would women be willing to enroll if informed consent statement presented this harms profile?



Conclusions

RCTs would not measure most harms that differed by mode of delivery well or at all

They would under-represent harms of cesarean section and over-represent harms of vaginal birth

Large multi-site RCT not a data panacea

Systematic reviews limited to such studies would distort the truth



Recommendations

- improve RCTs, whenever possible (e.g., trial size, measures, follow-up, reporting)
- in primary studies & systematic reviews, provide balanced attention to benefits & harms; include all meaningful outcomes
- in protocols, identify way to measure each outcome of interest: best feasible design
- in abstracts and reviews, specify areas of known and unknown uncertainty (need guidance in *Cochrane Handbook*)
- in reviews, clarify ways to improve future primary studies
- continue to strengthen quality of non-randomized studies and systematic reviews that include them

