Institution:
University of Cambridge

Unit of Assessment:
UoA1

Title of case study:
Caesarean section and the risk of perinatal death

1. Summary of the impact (indicative maximum 100 words)

Smith identified four novel findings around the relationship between caesarean section and perinatal death (i.e. stillbirth or neonatal death). 1. Vaginal birth after previous caesarean had a low absolute risk of death, but the risk was lower still with planned caesarean delivery. 2. The second twin had a higher risk of death at term. 3 Caesarean section was associated with an increased future risk of stillbirth. 4. Use of prostaglandins to induce labour in women with a previous caesarean increased the risk of death. The studies subsequently led to changes in national and international clinical guidelines, which remain current.

2. Underpinning research (indicative maximum 500 words)

Professor Gordon Smith, Department of Obstetrics & Gynaecology at University of Cambridge from 1st September 2001, has had the risks and benefits of Caesarean section as a major theme of his research group. All of the research cited below was the result of Smith's original ideas and he initiated all the studies.

Smith's group's JAMA paper of 2002 [1] reported a high quality study of over 300,000 births at term which was the first to address the risk of perinatal death among women with a previous caesarean section which focused on delivery related deaths at term. Previous studies had included deaths at preterm gestational ages and deaths unrelated to mode of delivery and their findings had been extrapolated to inform the risks associated with vaginal birth at term. However, Smith's research was able to demonstrate that the inclusion of preterm losses and deaths unrelated to mode of delivery in previous studies led to two sources of error (i) an overestimation of the absolute risk of death with all modes of delivery, and (2) an underestimation of the relative risk of death associated with attempted vaginal delivery.

Smith's BMJ paper of 2002 [2] reported a high quality study of over 4,500 twin births using nationally collected NHS data which was the first rigorous analysis of the risk of death related to birth order in twins. Previous studies had failed to confine analyses to deaths which were truly related to mode of delivery. Moreover, all previous large scale studies had used statistical tests which assumed statistical independence; i.e. there was an assumption that the two twins were not related and drawn at random from the population. Smith reported that this assumption was self-evidently flawed and the use of statistical tests based on this assumption resulted in biased (underestimated) risks to the second twin. The 2002 BMJ paper [1] reported an increased risk of death to the second twin using Scottish data, and subsequent research published in the 2007 BMJ paper [3] applied similar methods and confirmed the same finding in births from England and Wales.

Smith's Lancet paper of 2003 [4] was the first report of an association between previous caesarean section and future stillbirth, analysing ~120,000 second births in Scotland, 1992-1998. The finding was subsequently confirmed by analysis of the next 3 years of data (1999-2001) from Scotland (see Am J Epidemiol 2007;165:194-202), thus essentially eliminating the possibility that Smith's research published in the Lancet report was a chance finding. Further research and meta-analyses have also confirmed the association (Lancet. 2011;377:1331-40, Supplementary Web Appendix & PLoS One 2013;8(1):e54588).

Smith's group's research published in the BMJ paper of 2004 [5] was the first to show that use of prostaglandins to induce labour among women with a previous caesarean section increased the risk of delivery-related perinatal death. Moreover, it demonstrated that, although rates of uterine rupture among women with a previous caesarean section were similar in different sized obstetric units, delivery related perinatal death was more frequent in low throughput units.

The above research involved some innovative methodologies. For example, the 2003 Lancet paper

[3] described the first use of Cox proportional hazards modelling to assess stillbirth risk and the 2002 BMJ paper [1] described the first use of conditional logistic regression in the comparison of death rates in first and second twins. These methods have been adopted in multiple subsequent studies by other researchers. Two of the five papers have been cited by >100 subsequent publications and the other three have been cited 30, 40 & 50 times, which should be interpreted in the context that the leading specialist journals in the field have impact factors of ~4.

3. References to the research (indicative maximum of six references)

1. Smith GC, Pell JP, Cameron AD, Dobbie R. Risk of perinatal death associated with labor after previous cesarean delivery in uncomplicated term pregnancies. JAMA 2002;287:2684–90. [125 citations]
2. Smith GC, Pell JP, Dobbie R. Birth order, gestational age, and risk of delivery related perinatal death in twins: retrospective cohort study. BMJ 2002;325:1004. [40 citations]
3. Smith GCS, Fleming K, White IR. Birth order of twins and the risk of delivery-related perinatal death in England, Northern Ireland and Wales, 1994-2003. BMJ 2007;334:576. [30 citations]
4. Smith GCS, Pell JP, Dobbie R. Caesarean section and risk of unexplained stillbirth in subsequent pregnancy. Lancet 2003;362:1779–84. [151 citations]
5. Smith GCS, Pell JP, Pasupathy D, Dobbie, R Factors predisposing to perinatal death related to uterine rupture during attempted vaginal birth after caesarean section: retrospective cohort study. BMJ 2004:329:375-377. [50 citations]

4. Details of the impact (indicative maximum 750 words)

The JAMA paper of 2002 had reported that although planned repeat caesarean section was associated with a lower risk of perinatal death during delivery, the absolute risk of attempting vaginal birth was lower than had previously been reported and was similar to that of women in their first pregnancy. Prior to this publication, much higher absolute risks of death had been used for counselling (e.g. see an editorial in NEJM 2001;**345**:54-55). Following on from Smith's programme of research, counselling both in the UK and internationally has moved to quoting the much lower rates reported first in the JAMA paper and confirmed in subsequent analyses. The direct influence of Smith's work is demonstrated by his results in the JAMA paper being extensively discussed in the RCOG Guideline.[1] The estimates of absolute risk from the JAMA paper are presented in Table 2 of the current US Guideline published in 2010.[2] The Canadian guideline published in 2005 devotes a full paragraph to summarising the results of this paper.[3] All three guidelines have been current for all or part of the interval from 2008 to 2013.

The 2002 BMJ paper was the first to report an increased risk of perinatal death among vaginally delivered second twins at term in Scotland. The 2007 paper confirmed that the same association was present in England and Wales. The importance of Smith's research in identifying the increased risk for second twins is discussed in the NICE Guideline, CG132 Caesarean section (2011).[4]

The Lancet paper of 2003 had reported an increased risk of stillbirth among women with a previous caesarean section and as a result of this research, there has been a widespread change in the counselling of women considering delivery by caesarean section, as evidenced by changes in clinical guidelines. For example, a whole paragraph is devoted to describing the findings of this paper in the 2011 NICE Guideline, CG132 Caesarean section (2011, page 180).[4] Another practical consequence of this research was that among women with a previous caesarean section, it became possible to predict that there would be a significant risk of antepartum stillbirth associated with a decision to have a vaginal birth. Both the current RCOG and ACOG Guidelines comment on this risk.[1,2] Although this was seen as controversial at the time (see correspondence in Lancet 2004;363:402), the prediction was subsequently confirmed by a large scale US study by the NICHD Maternal-Fetal Medicine Units Network (Landon et al NEJM 2004;351:2581-2589).

The 2004 BMJ paper was the first to report an increased risk of perinatal death due to uterine rupture associated with induction of labour using prostaglandins. These findings are discussed in detail in the current RCOG Guideline, Birth after previous caesarean section (2007).[1] A whole

paragraph is devoted to the results of this study in the NICE Guideline, CG70 Induction of Labour (2008).[5] The study has been less quoted internationally as different prostaglandin preparations tend to be used in North America.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Birth after previous caesarean section: Guideline No 45. Royal College of Obstetricians & Gynaecologists, London, UK. February 2007.
See http://www.rcog.org.uk/files/rcog-corp/GTG4511022011.pdf
Note: although published in 2007, this guideline remained current from July 2008 onwards and was accessed on 25 July 2013 from the following site:
http://www.rcog.org.uk/womens-health/clinical-guidance/birth-after-previous-caesarean-birth-green-top-45

2. The American College of Obstetricians and Gynecologists Practice Bulletin: Vaginal birth after previous cesarean delivery. *Obstetrics & Gynecology* 2010;**116**:450-463.

3. Society of Obstetrics and Gynecology, Canada, Guideline Guidelines for Vaginal Birth After Previous Caesarean Birth, number 155.
Note: although published in 2005, this guideline remained current from July 2008 onwards and was accessed on 25 July 2013 from the following site:
http://www.sogc.org/guidelines/public/155E-CPG-February2005.pdf

4. National Institute of Clinical Excellence. CG132 Caesarean section. November 2011.
See http://www.nice.org.uk/nicemedia/live/13620/57162/57162.pdf

5. National Institute of Clinical Excellence. CG70. Induction of labour. July 2008.
See http://www.nice.org.uk/nicemedia/live/12012/41255/41255.pdf