Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: K: Progesterone does not prevent preterm birth in twin pregnancy (STOPPIT study)

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

Impact: Health and welfare; public policy; the work led to UK and international guidelines advising against progesterone use to prevent preterm birth in twin pregnancy.

Significance: Thousands of women now avoid this unpleasant procedure annually, with a saving to the NHS of £25M.

Beneficiaries: Pregnant women, policy-makers, the NHS and healthcare-providers.

Attribution: The work was initiated by a five-centre UK collaborative group including UoE. Data analysis, interpretation and translation into practice were led by Jane Norman, UoE.

Reach: The data are cited in guidelines and have changed clinical practice on three continents: Europe (NICE), North America and Australasia. Applies to 11,000 women annually in UK alone.

2. Underpinning research (indicative maximum 500 words)

Professor Jane Norman (Professor of Maternal and Fetal Health, UoE, 2008–present), with UoE Co-Is Dr Sarah Cooper (UoE 2001–2003) and Professor Andrew Calder (UoE 1987–2009; now Emeritus), initiated (while based in Glasgow) the STOPPIT trial. Following relocation to Edinburgh (2008) Norman undertook trial data analysis and showed definitively that progesterone does not prevent pre-term birth in twin pregnancy.

Over 22,000 twins are born in the UK each year. Babies from twin pregnancy have a three-times higher chance of dying during gestation or in the first week of life (perinatal mortality), and this excess in perinatal mortality is largely owing to increased rates of preterm birth.

Progesterone prevents preterm birth in other scenarios where women are at high risk. Before the STOPPIT study, many clinicians had started to use progesterone for the prevention of preterm birth in twin pregnancy. This would have involved treatment of 11,000 women per year in the UK, and many more worldwide. On the basis of this, and the fact that women with twin pregnancy are at especially high risk, Norman conceived the "STOPPIT" study to determine whether progesterone is effective in preventing preterm birth in twins. The project was funded by a Chief Scientist Office grant awarded in 2004 to a five-centre collaborative group including UoE, and was led by Norman, who performed the analysis after having moved to UoE in 2008.

The group conducted a double-blind, placebo-controlled trial, recruiting 500 women with twin pregnancy from nine clinics specialising in the management of twin pregnancy. Women were randomised, in permuted blocks of randomly mixed sizes, either to daily vaginal progesterone gel 90 mg (*n*=250) or to placebo gel (*n*=250) for 10 weeks from 24 weeks' gestation. All study personnel and participants were masked to treatment assignment for the duration of the study. The primary outcome was delivery or intrauterine death before 34 weeks' gestation. Analysis was by intention to treat. Additionally the group undertook a meta-analysis of published and unpublished data to establish the efficacy of progesterone in the prevention of early (<34 weeks' gestation) preterm birth or intrauterine death in women with twin pregnancy, and an economic evaluation.

The study found that the combined proportion of intrauterine death or delivery before 34 weeks of pregnancy was 24.7% (61/247) in the progesterone group and 19.4% (48/247) in the placebo group (odds ratio [OR] 1.36, 95% confidence interval [CI] 0.89–2.09; *p*=0.16). The rate of adverse

events did not differ between the two groups. The meta-analysis confirmed that progesterone does not prevent early preterm birth in women with twin pregnancy (pooled OR 1.16, 95% CI 0.89–1.51) [3.1].

The economic evaluation showed that giving progesterone prophylaxis to women with twin pregnancy is not cost-effective, with a mean excess cost in the progesterone group of £2,059 per woman treated [3.2].

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

3.1 Norman J, Mackenzie F, Owen P, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. Lancet. 2009;373:2034–40. DOI: 10.1016/S0140-6736(09)60947-8. *[cited 100 times; Google scholar, 24 Jun 2013]*.

3.2 Eddama O, Petrou S, Regier D,…Norman J. Study of progesterone for the prevention of preterm birth in twins (STOPPIT): Findings from a trial-based cost-effectiveness analysis. Int J Technol Assess Health Care. 2010;26:141–8. DOI: 10.1017/S0266462310000036.

Grant:

Norman J, Mackenzie F, Owen P, et al. Double blind randomised placebo controlled study of progesterone for the prevention of preterm labour in twins (STOPPIT). Chief Scientist Office, Scottish Executive, 2004–2008. £224,062. *[This grant was awarded to a UK collaborative group, led by Professor Jane Norman, Edinburgh Co-Is Professor Andrew Calder and Dr Sarah Cooper, and managed by the University of Glasgow. Participants were recruited when Jane Norman was at the University of Glasgow. Data analysis and interpretation were performed by Jane Norman, Professor of Maternal and Fetal Health at UoE after her appointment in 2008.]*

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

Impact on public policy and services
The STOPPIT study showed that progesterone was ineffective in women with twin pregnancy, and has led to clear guidelines published in 2011 or 2012 from three continents (Europe (NICE), North America and Australasia [5.1–5.6, 5.7]) that progesterone should not be used for this purpose.

Impact on health and welfare
The research has changed clinical practice internationally for women with twin pregnancy (e.g. in Canada, Australia [5.8]). In the UK alone, the research has prevented the ineffective treatment of 11,000 women per year.

Daily administration of a vaginal gel in pregnancy (as advocated in women with singleton pregnancy at high risk of preterm birth) is unpleasant. The STOPPIT study has stopped this happening. Additionally, all drugs administered during pregnancy have the potential for teratogenic effects, with these effects sometimes not being immediately apparent (e.g., stilboestrol). Although there are no known adverse effects of progesterone at the stage of pregnancy used for preterm labour prevention, the STOPPIT study has prevented risk of exposure to any covert long-term adverse effects.

Impact on the economy
The excess cost of treating women with twin pregnancy with progesterone was £2,334 per patient, with no clinical benefit. On a UK population basis alone, the excess cost of treating women with twin pregnancy with progesterone was £25M (2008 prices). These costs are now avoided.

Impact on society
Public awareness and public involvement in research has been increased by reference to the work in the media including the BBC News website on 10th June 2009 [5.9].

Additionally, the data were referred to in a public lecture given by Jane Norman “The mysteries of

birth – far from elementary my dear Watson" in October 2010, which has been accessed over 2,700 times on YouTube [5.10].

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

5.1 NICE Clinical Guideline on Multiple Pregnancy (2011). The management of twin and triplet pregnancies in the antenatal period. http://www.nice.org.uk/nicemedia/live/13571/56422/56422.pdf.

5.2 Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. Am J Obstet Gynecol. 2012;206:376–86. DOI: 10.1016/j.ajog.2012.03.010.

5.3 Committee on Practice Bulletins—Obstetrics, The American College of Obstetricians and Gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. Obstet Gynecol. 2012;120:964–73. DOI: 10.1097/AOG.0b013e3182723b1b.

5.4 Di Renzo G, Roura L, Facchinetti F, et al. Guidelines for the management of spontaneous preterm labor: identification of spontaneous preterm labor, diagnosis of preterm premature rupture of membranes, and preventive tools for preterm birth. J Matern Fetal Neonatal Med. 2011;24:659–67. DOI: 10.3109/14767058.2011.553694.

5.5 The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (2010). C-Obs 29 (b). Progesterone: Use in the second and third trimester of pregnancy for the prevention of preterm birth. http://www.ranzcog.edu.au/component/docman/doc_view/962-c-obs-29b-progesterone-use-in-the-second-trimester-and-third-trimester-of-pregnancy.html?Itemid=341.

5.6 González R. Prenatal administration of progesterone for preventing preterm birth in women considered at risk of preterm birth: RHL commentary (last revised: 1 December 2009). The WHO Reproductive Health Library; Geneva: World Health Organization. http://apps.who.int/rhl/pregnancy_childbirth/complications/preterm_birth/cd004947_gonzalezr_com/en/.

5.7 NICE, Preterm Labour and Birth, Guideline Development Group Membership List. http://www.nice.org.uk/nicemedia/live/14004/64412/64412.pdf.

5.8 Letter from the Head, Department of Obstetrics and Gyaecology, Monash University, Australia. *[Available on request. Confirms that the work informed changes to clinical practice guidelines in Victoria, Australia, changing the recommended care for women with twin pregnancy.]*

5.9 BBC News website (10 Jun 2009). Multiple birth differences found. http://news.bbc.co.uk/1/hi/scotland/edinburgh_and_east/8093621.stm.

5.10 The mysteries of birth – far from elementary my dear Watson (2010). http://www.youtube.com/watch?v=TC43j2UJ-GI.