Institution: University of Birmingham

Unit of Assessment:UoA1

Title of case study: Establishing evidence-based clinical guidelines for multiple pregnancy.

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

Perinatal morbidity and mortality is high in the UK compared to many developed countries. Serious congenital diseases may be detected in-utero and in some of these diseases fetal therapy may significantly improve outcome. The Fetal Research Group in Birmingham led by Professor Mark Kilby has made major contributions in improving knowledge of prevalence and of best management of major causes of fetal death, especially complications arising in monochorionic twins. These are cases where twins share the same placenta, in which complications are common and can lead to handicap and brain development problems as well as high fetal mortality rates. Critical appraisal of the evidence and novel research into these disordershasclearly evaluated therapeutic approaches and clinical management. This work has ultimately allowed development and implementation of evidence-based recommendations on managing multiple pregnancies for the first time in the UK.

2. Underpinning research (indicative maximum 500 words)

Fetal disease contributes to perinatal (the period immediately before and after birth) morbidity and mortality in the UK and worldwide. A large amount of disease is caused by birth defects (normally structural), although up to 15% of problems are amenable to prenatal treatment and therapy, significantly improving outcome and long-term morbidity. Research into the mechanisms underlying conditions that affect fetal health, as well as the evaluation of potential fetal therapies, has been led by Professor Mark Kilby at the University of Birmingham (at UoB since 1995) over the past fifteen years.

Identical (monozygotic) twins that share the same placenta are known as 'monochorionic' twins. These pregnancies have high rates of morbidity and mortality for the fetus; this is because of a shared placental circulation which can cause disproportionate blood supply to one of the twins. This may result in 'twin-to-twin transfusion syndrome', where one twin has a decreased blood volume (potentially leading to restricted growth or brain development) and the other has an abnormally high blood volume (which can strain their heart and lead to heart failure). In these cases, the risk of one or more twins dying is up to 90%. Key systematic reviews delivered by Professor Mark Kilby has highlighted the evidence-based risks of co-twin demise and brain damage in the survivors of co-twin demise in monochorionic twins and have identified the optimal prenatal management in such scenarios [1]. Related work over a series of studies led by Professor Kilby has demonstrated that fetoscopic laser ablation – ain-utero technique involving laser surgery to coagulate and reduce abnormal blood vessels – is the superior treatment in these complications [2]. This is in comparison with other techniques which simply remove some of the excess amniotic fluid with a needle (amniodrainage) to reduce the pressure in the womb. Further appraisal of a dataset from Birmingham has also highlighted that good outcomes can be achieved using fetoscopic laser ablation even where the surgeon is less familiar with the technique but is supported by appropriate training [3].

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

1. Hillman SC, Morris RK, Kilby MD. Co-twin prognosis after single fetal death: a systematic review and meta-analysis. Obstet Gynecol. 2011;18(4):928-40. *doi: 10.1097/AOG.0b013e31822f129d*

2. Fox C, Kilby MD, Khan KS. Contemporary treatments for twin-twin transfusion syndrome. Obstet Gynecol. 2005;105(6):1469-77. *PMID:15932845*

3. Morris RK, Selman TJ, Harbidge A, Martin WI, Kilby MD. Fetoscopic laser coagulation for severe twin-to-twin transfusion syndrome: factors influencing perinatal outcome, learning curve of the procedure and lessons for new centres. BJOG. 2010;117(11):1350-7. *doi: 10.1111/j.1471-0528.2010.02680.x*

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

Fetal therapy is a relatively new subspecialty that allows fetal and perinatal morbidity and mortality to be reduced. Such treatment is concentrated in specialist centres and there is a strong call amongst maternal care specialists and national services for such interventions to be evidenced-based [1]. Such interventions have to be targeted at congenital conditions which are potentially fatal but have a reversible course if treated or the long term consequences of fetal disease can be ameliorated by in-utero intervention. The Fetal Medicine Centre led by Professor Kilby and affiliated to the University of Birmingham has been instrumental in critically appraising evidence for accurate diagnosis of fetal conditions and systematically evaluating outcomes of prenatal intervention. This is particularly evident in their contribution to clinical guidelines and practice in management of monochorionic twins.

Monochorionic twins have conjoining of the feto-placental circulations and 'share' a single placenta. This form of twinning is associated with a high perinatal mortality (8%). Complications, such as single twin demise (death) and twin to twin transfusion syndrome (which complicates 15% of monochorionic twin pregnancies) have high fetal mortality rates. Handicap and brain development problems in survivors complicate up to 15% of survivors, even with treatment.

Work led by Professor Mark Kilby has been pivotal in critically evaluating risks of single twin demise in monochorionic twins and outlining optimal investigation and management. In addition, in-utero treatment of severe twin to twin transfusion syndrome is complex and has been controversial. Critical appraisal of the evidence base informing management strategies for this morbid disease have been incorporated by the Cochrane Pregnancy and Childbirth Group into guidance on interventions to treat twin to twin transfusion syndrome [2].

Alongside this, Professor Kilby has been instrumental in ensuring that his research in monochorionic twins has been incorporated into national and international discussion and further peer-reviewed clinical guidance. In 2005, Professor Kilby convened an international scientific working group that held a week long symposium at the Royal College of Obstetricians and Gynaecologists (RCOG) to gather current expertise and evidence relating to the management of multiple pregnancies. Expert opinion was published as a discussion vignette [3] which then formed the basis and stimulus to the creation of a further peer reviewed, evidence-based clinical guideline.

To achieve this, Prof Kilby co-chaired the working group that produced a set of RCOG "Green-top guidelines" in 2008[4]. This type of guidance has been specifically developed by RCOG to provide systematically developed recommendations that assist clinicians and patients in making decisions about appropriate treatment for specific, specialist conditions. They are concise documents, providing specific recommendations on focused areas of clinical practice. In this case, the aim of the guidelines was *"to describe and, if possible, quantify the problems associated with monochorionic placentation and to identify the best evidence to guide clinical care, including routine fetal surveillance and treatment of complications at secondary and tertiary levels."*

It was important to follow this up with official national recommendations that would more formally influence practice on a broader scale. Typically this is achieved via the National Institute for Health and Care Excellence (NICE), which sets accepted practice for patient healthcare, used by groups ranging from NHS, Local Authorities, employers, voluntary groups and others involved in delivering care or promoting wellbeing.Prof Kilby was chairman of the national, multidisciplinary NICE Clinical Guidelines Group (within the National Collaborating Centre for Women's and Children's Health) which produced the 2011 national guidance for the management of twin and triplet pregnancies [5]. This was the first time NICE had published detailed recommendations for healthcare professionals on managing multiple pregnancy, and therefore remains a crucial set of information informing current and future practice. These data were also summarised in a vignette for healthcare professionals to help ensure their further dissemination and impact on clinical practice [6].

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

1. NHS England Standard Contract for Fetal Medicine. 2013. http://www.england.nhs.uk/wp-content/uploads/2013/06/e12-fetal-medi.pdf
2. Roberts D, Neilson JP, **Kilby M.D**, Gates S. Interventions for the treatment of twin-twin

transfusion syndrome. Cochrane Database Syst Rev. 2008;(1):CD002073. *doi: 10.1002/14651858.CD002073.pub2.*
3. RCOG study group statement. Consensus views arising from the 50th Study Group: Multiple Pregnancy. 2006. London, RCOG Press.http://www.rcog.org.uk/files/rcog-corp/uploaded-files/StudyGroupConsensusViewsMultiplePregnancy.pdf.ISBN-10: 1904752225.
4.RCOG Guidelines for the management of monochorionic twin pregnancies, 2008 http://www.rcog.org.uk/files/rcog-corp/uploaded-files/T51ManagementMonochorionicTwinPregnancy2008a.pdf.
5. Multiple pregnancy: The management of twin and triplet pregnancies in the antenatal period Issued: September 2011. NICE clinical guideline 129. *www.nice.org.uk/niceme* .
6. Visintin C, Mugglestone MA, James D, **Kilby MD**; Guideline Development Group.Antenatal care for twin and triplet pregnancies: summary of NICE guidance.BMJ. 2011;343:d5714. *doi: 10.1136/bmj.d5714.*