

<b>Institution:</b> University of Warwick		
<b>Unit of Assessment:</b> UOA1		
<b>Title of case study:</b> Recurrent Pregnancy Loss: informing clinical management and professional guidance, and improving patient care through advocacy and awareness		
<b>Period when the underpinning research was undertaken:</b> 1 October 2011- 31 December 2020		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Professor Jan Brosens	Chair of Obstetrics and Gynaecology; Honorary Consultant Gynaecologist at University Hospital Coventry and Warwickshire NHS Trust.	01/05/2011- present
Professor Siobhan Quenby	Professor of Obstetrics; Honorary Consultant Obstetrician at University Hospital Coventry and Warwickshire NHS Trust.	01/02/2010- present
<b>Period when the claimed impact occurred:</b> 1 August 2013 – 31 December 2020		
<b>Is this case study continued from a case study submitted in 2014?</b> N		
<b>1. Summary of the impact</b> (indicative maximum 100 words)		
<p>Research by Professors Jan Brosens and Siobhan Quenby that focused on early embryo-endometrial interactions demonstrated that recurrent pregnancy loss (RPL) is linked to implantation checkpoint failure. This has underpinned the development and evaluation of novel tests and treatments which allow for targeted, individualised care for thousands of patients at Warwick's Implantation Research Clinic (nearly 3,500 – with 2,000 infants born - since August 2013) as well as at facilities in many other countries. The research has led to improved clinical care across the world by informing guidelines of professional organisations and training and education of healthcare professionals. It has underpinned the creation of a national centre of excellence in 2016, the Tommy's National Centre for Miscarriage Research, together with partners in Birmingham and London, building research capability, supporting patient-centred care (24,000 women since April 2016), improving patient advocacy and raising public awareness of RPL (2,000,000 visitors to the website per month).</p>		
<b>2. Underpinning research</b> (indicative maximum 500 words)		
<p><b>Background:</b> Miscarriage is the most prevalent disorder of pregnancy, affecting over 200,000 women in England and Wales each year. Approximately 15% of all pregnancies end in miscarriage. Recurrent pregnancy loss (RPL), clinically defined as multiple consecutive losses, increases the risk of adverse outcome of a subsequent ongoing pregnancy: adjusting for maternal age, the odds ratio for miscarriage increases from 1.5 after one loss to 2.2 and 4 after two and three consecutive losses, respectively. There are few effective interventions for this devastating condition that has been attributed to a spectrum of subclinical disorders, ranging from thrombophilia to endocrine and immunological disorders. A body of research led by Brosens and Quenby at Warwick from 2011 challenged this entrenched disease paradigm and addressed the knowledge gap in an effort to improve live-birth rates.</p> <p><b>Identification of an 'implantation checkpoint':</b> In collaboration with University Medical Centre Utrecht, Brosens and Quenby demonstrated that differentiated endometrial stromal cells</p>		

(decidual cells) are biosensors of embryo quality that either promote further implantation or facilitate rapid rejection in response to excessive embryo-derived protease activity [3.1]. These observations pointed towards the existence of an 'implantation checkpoint' to limit maternal investment in abnormal but highly invasive embryos. Analysis of primary cultures and timed biopsies demonstrated that RPL is linked to aberrant decidualization (i.e. changes to the cells of the endometrium in preparation for pregnancy). Loss of this implantation checkpoint provides a compelling explanation for the characteristic superfertility (i.e. rapid conceptions) associated with RPL [3.2]. Decidual cells also drive the transformation of the cycling endometrium into a semi-permanent state that accommodates the placenta throughout pregnancy. Ablation in mice of decidual genes deregulated in RPL, such as *Sgk1*, recapitulates the sequence of events leading to miscarriage [3.3].

Further research into underlying pathological mechanisms: In 2015, genome-wide DNA methylation analysis of primary cultures demonstrated loss of a conspicuous epigenetic stem cell signature in RPL patients. Colony-forming unit assays confirmed that RPL is associated with lack of (bone marrow-derived) mesenchymal stem cells (MSC) in the endometrium, with the level of depletion correlating to the number of previous miscarriages [3.4]. In 2016, Brosens and Quenby demonstrated that decidualization starts with an acute cellular stress response leading to the emergence of specialist decidual cells as well as acute senescent cells that are progesterone-resistant and abundantly secrete inflammatory mediators and extracellular matrix remodelling factors [3.5, 3.6]. Decidual cells then engage uterine natural killer (uNK) cells to eliminate their senescent counterparts, enabling formation of a robust decidual matrix in pregnancy [3.5]. From 2018, high-throughput single-cell transcriptomic analysis identified highly selective marker genes of decidual cells and senescent decidual cells. Analysis of clinical samples provided compelling evidence that MSC deficiency in RPL results in an excessive peri-implantation pro-senescent decidual response, not only disabling the implantation checkpoint but also predisposing for a feto-maternal interface intrinsically prone to breakdown [3.6].

Novel disease paradigm: The discovery that MSC and uNK cells are homeostatic regulators of the decidual response prior to conception has led to a novel disease paradigm, positing that risk of euploid (where there is an equal number of all the chromosomes) miscarriage is determined by the frequency of cycles with a pro-senescent decidual response, and opened up new strategies for the prediction and prevention of RPL.

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

- [3.1] **Brosens, JJ, Salker, MS**, Teklenburg, G, Nautiyal, J, **Salter, S, Lucas, ES**, Steel, JH, **Christian, M, Chan, YW**, Boomsma, CM., **Moore, JD, Hartshorne, GM**, Šučurović, S, Mulac-Jericevic, B, Heijnen, CJ., **Quenby, S**, Koerkamp, MJ., Holstege, FCP, **Shmygol, A** and Macklon, NS. (2014) Uterine selection of human embryos at implantation. *Scientific Reports*, 4, 3894. doi:10.1038/srep03894
- [3.2] **Salker MS**, Nautiyal J, Steel JH, Webster Z, **Sučurović S**, Nicou M, Singh Y, **Lucas ES, Murakami K, Chan YW, James S, Abdallah Y**, Christian M, Croy BA, Mulac-Jericevic B, **Quenby S, Brosens JJ** (2012). Disordered IL-33/ST2 activation in decidualizing stromal cells prolongs uterine receptivity in women with recurrent pregnancy loss. *PLoS One*, 7(12), e52252. doi:10.1371/journal.pone.0052252
- [3.3] Salker MS, Christian M, Steel JH, Nautiyal J, Lavery S, Trew G, Webster Z, Al-Sabbagh M, Puchchakayala G, Föller M, Landles C, Sharkey AM, **Quenby S**, Aplin JD, Regan L, Lang F, **Brosens JJ** (2011). Deregulation of the serum- and glucocorticoid-inducible kinase SGK1 in the endometrium causes reproductive failure. *Nat Med*, 17(11), pp. 1509-13. doi: 10.1038/nm.2498
- [3.4] **Lucas ES, Dyer NP, Murakami K**, Lee YH, **Chan YW, Grimaldi G, Muter J, Brighton PJ, Moore JD, Patel G**, Chan JK, Takeda S, Lam EW, **Quenby S, Ott S, Brosens JJ** (2016). Loss of Endometrial Plasticity in Recurrent Pregnancy Loss. *Stem Cells*, 34(2), pp. 346-356. doi:10.1002/stem.2222
- [3.5] **Brighton PJ, Maruyama Y, Fishwick K, Vrljicak P, Tewary S, Fujihara R, Muter J, Lucas ES**, Yamada T, Woods L, **Lucciola R**, Hou Lee Y, Takeda S, Ott S, Hemberger M,

**Quenby S, Brosens JJ** (2017). Clearance of senescent decidual cells by uterine natural killer cells in cycling human endometrium. *eLife*, 6, e31274. doi:10.7554/eLife.31274

[3.6] **Lucas ES, Vrljicak P, Muter J, Diniz-da-Costa MM, Brighton PJ, Kong CS, Fishwick K, Odendaal J, Ewington LJ, Quenby S, Ott S, Brosens JJ** (2020). Recurrent pregnancy loss is associated with a pro-senescence decidual response during the peri-implantation window. *Communications biology*, 3(1), 37. doi:10.1038/s42003-020-0763-1

### Grants

S. Quenby and J. Brosens (Co-Is), in collaboration with the University of Birmingham and Imperial College London and their partner hospitals. Tommy's National Centre for Miscarriage Research; Tommy's and the University Hospital Coventry and Warwickshire National Health Service Trust; 2016-2021, GBP1,028,580

S. Quenby (PI). Tommy's reproductive health biobank; MRC, 2017-2021, GBP1,156,059

J. Brosens (PI). Wellcome Investigator Award 'Cellular dynamics and regulatory networks controlling endometrial remodelling associated with recurrent miscarriage'; Wellcome Trust, 2018-2023, GBP1,281,629

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

Brosens and Quenby's research on the role of early embryo-endometrial interactions and RPL has had an impact on practitioners, patients and the public, in the UK and globally. It has addressed a previously unrecognised and unmet need for clinical care for many thousands of women by (i) establishing a dedicated research clinic, (ii) developing novel tests and treatment strategies, (iii) improving clinical guidelines and CPD, and (iv) through public engagement and patient advocacy.

#### Impact on practitioners: improving and guiding clinical management

(i) Specialised care in a dedicated facility: Since 2012 Brosens and Quenby have led a dedicated Implantation Research Clinic, a joint initiative between Warwick Medical School and University Hospitals Coventry and Warwickshire NHS Trust that provides a unique research-led service for women with complex reproductive histories. Between August 2013 and July 2020, 3,423 patients attended the clinic from across the UK and abroad including Ireland, Belgium, Germany, Sweden, France, Spain, Malta, Switzerland and the USA. Over 2,000 babies were born following research-led treatment to couples who had previously experienced multiple physically and emotionally difficult miscarriages. The clinic addressed, often for the first time, couples' questions and fears, formulating a treatment plan and offering individualised support before and during pregnancy.

(ii) Developing and evaluating novel treatments and strategies: Brosens and Quenby have developed three tests to support better clinical diagnosis and treatment:

In 2016, Quenby optimised **an accurate, rapid method of counting uNK cells using digital image analysis** [5.1] that has informed the development of personalised approaches to guide clinical management for repeated miscarriage or failure of IVF. This has resulted in "many miracle babies" [5.2], not only in the Research Implantation Clinic but also specialist clinics around the world, including China, Denmark and Australia. Gavin Sacks, clinical director of IVF Australia, developed the Bondi Protocol, an inexpensive treatment for women who may have an immune problem causing either repeated IVF failure or repeated miscarriages. A combination of prednisolone and clexane, taken from the start of an IVF cycle or as soon as a pregnancy has been diagnosed, is continued until at least 12 weeks gestation. Dr Sacks states that Brosens and Quenby's research has been "invaluable when developing, reviewing and updating the Bondi protocol. This has been used on approximately 700 couples... between August 2013 and July 2020." [5.3]

In 19/08/2020, Brosens patented (UKIPO patent 1911947.8) **a biomarker-based test to quantify decidual cells and senescent decidual cells** [3.6]. This will be used to screen women for their risk of miscarriage and to guide pre-pregnancy sitagliptin treatment to reverse excessive decidual senescence. Sitagliptin, a DPP4 inhibitor that is already licensed as an oral

antidiabetic drug, was found to be effective in enhancing endometrial plasticity during the implantation window in RPL patients in Warwick's Sitagliptin for Implantation (SIMPLANT) study (2016-2019) - the first evidence that this is possible pharmacologically [5.4]. A large-scale follow-up RCT planned for 2021 is now expected to be delayed due to COVID-19.

In 2017-2018, Quenby optimised **a chronic endometritis test** based on immunohistochemical analysis of CD138+ cells followed by digital image analysis. The Chronic Endometritis and Recurrent Miscarriage (CERM) trial, a GBP1,800,000 multicentre NIHR/ MRC-funded RCT aimed at evaluating the efficacy of pre-pregnancy doxycycline in RPL patients who tested positive for chronic endometritis, was launched in December 2019.

(iii-a) Addressing gaps in clinical guidelines: As Coordinator of the European Society of Human Reproduction and Embryology (ESHRE) Early Pregnancy Special Interest Group from 2014 to 2018, Quenby co-authored the 2017 evidence-based ESHRE guidelines on RPL [5.5]. These draw on Warwick's research and advocate the need for supportive, evidenced-based clinics in the context of a dearth of evidenced-based investigations and treatments for RPL. ESHRE has a significant influence on international clinical practice through its annual conference and training across Europe for over 10,000 embryologists, doctors, nurses, and scientists.

(iii-b) Contributing to training and continued professional development: As Executive Committee Member of the Association of Early Pregnancy Units (AEPU) (2014), Quenby supported the increased awareness of RPL and training for doctors, nurses, ultrasonographers, midwives and support staff from over 200 NHS Early Pregnancy Units, and presented Warwick's research to 300-plus professionals at AEPU annual meetings. Quenby also lectures on the Royal College of Obstetricians and Gynaecologists (RCOG) educational and professional development courses; both Quenby and Brosens are mentors for academic trainees. As part of the Fetal Medicine Foundation's educational programme for healthcare professionals and parents, Quenby reached over 12,000 doctors from 150 countries (July 2020) improving understanding of the role of endometrial stem cells.

### **Impact on patients and public: improving health and well-being, advancing knowledge**

(iv-a) Establishing Tommy's National Miscarriage Research Centre: Tommy's is the UK's leading charity focused on premature birth, stillbirth and miscarriage. In 2016, Warwick was integral in launching Tommy's National Miscarriage Research Centre, a collaborative university/NHS model with the University of Birmingham, Imperial College London and their partner hospitals. The Centre enables women to access treatment and support, and participate in research studies; it has been instrumental in breaking the silence, stigma and lack of information around miscarriage. Tommy's CEO Jane Brewin states that without Warwick's research, "we would not have had the knowledge and understanding of recurrent miscarriage which has enabled the Tommy's National Centre for Miscarriage Research to provide 24,000 women access to treatment via four associated clinics" [5.6]. The research has directly informed Tommy's information and guidance to parents who have suffered from miscarriage via its website, social media platforms and phone line support, and Brosens and Quenby's scientific evidence is "a significant factor for the 2,000,000 people who visit the [web] site each month" [5.6].

(iv-b) Support for donor events and other campaigns: During the assessment period, Brosens and Quenby presented their research to a wide range of organisations such as GSK, Johnson & Johnson, Betty Messenger Charitable Foundation and Tumble Tots, as well as potential individual donors and social media influencers, at 11 Downing St and other London locations. Tommy's 2015 #misCOURAGE campaign encouraged sharing of experiences of miscarriage; it reached over 16,000,000 people on social media, with 7,000 women taking part in a survey and over 1,000 sharing their personal stories: "Our long journey started in 2008...I was referred to the research team at UHCW ... our beautiful healthy little boy Hughie was born in Feb 2017. We can't thank the research team enough as we believe that their study, which we took part in, helped us to conceive." Tommy's 2019 Tell Me Why? campaign uses Brosens' research on role of the endometrium and early pregnancy checkpoints to help couples understand the causes of recurrent miscarriage providing a valuable coping mechanism when embarking on a future



## Impact case study (REF3)

pregnancy; the animation and the video have had over 5,000 and 10,000 views respectively, as of 2 December 2019 [5.6].

(iv-c) Patient advocacy: Brosens and Quenby maintain a local (West Midlands) working group of patients who are/have been involved in pregnancy research and miscarriage trials. Amy Jackson, a former patient of the clinic and co-founder of Lily Mae Foundation, which supports parents who have lost a baby to miscarriage or stillbirth, says that “this group has been essential for bringing the patients’ voice to the forefront of research ideas from the beginning and shaping initial thinking” [5.7].

(iv-d) Engagement with the public: Brosens and Quenby increased understanding and changed attitudes to the causes of recurrent miscarriage through such vehicles as: the Fertility Show (2016 & 2017, attended by over 1,000 members of the general public); British Festival of Science 2019; webchats on Mumsnet (January 2016, [5.9]), Tommy’s Facebook live interview (February 2017, attended by 6,500 individuals) [5.6], Channel 4 News (October 2017), the Independent (3 March 2016) and many BBC national and regional radio programmes including Radio 4, Radio 5 Live, BBC Coventry and Warwickshire and Radio Scotland).

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

[5.1] Lash GE, Bulmer JN, Li TC, Innes BA, Mariee N, Patel G, Sanderson J, Quenby S, Laird SM. (2016). Standardisation of uterine natural killer (uNK) cell measurements in the endometrium of women with recurrent reproductive failure. *Journal of reproductive immunology*, 116, 50–59.

[5.2] Written statement from Director of the Assisted Reproductive Technology Unit, Faculty of Medicine, Chinese University of Hong Kong

[5.3] Written statement from Clinical Director IVF Australia.

[5.4] Tewary, S, Lucas, ES., Fujihara, R., Kimani, PK, Polanco, A., Brighton, PJ, Muter, J., Fishwick, KJ., Da Costa, M., Ewington, L. J., Lacey, L., Takeda, S., Brosens, J. J., & Quenby, S. (2020). Impact of sitagliptin on endometrial mesenchymal stem-like progenitor cells: A randomised, double-blind placebo-controlled feasibility trial. *EBioMedicine*, 51, 102597. doi:10.1016/j.ebiom.2019.102597 (Chosen by EBioMedicine as one of the 10 research highlights of 2020 – see: [https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964\(20\)30561-2/fulltext](https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30561-2/fulltext))

[5.5] ESHRE Guideline on the management of recurrent pregnancy loss

<https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Recurrent-pregnancy-loss.aspx>

[5.6] Written statement from Chief Executive, Tommy’s, the UK’s leading baby charity focused on premature birth, stillbirth and miscarriage

[5.7] Written statement from Lily Mae Foundation Founder

[5.8] Mumsnet webchat: [https://www.mumsnet.com/Talk/mumsnet\\_live\\_events/2557552-Webchat-with-Professor-Siobhan-Quenby-on-recurrent-miscarriage-on-Friday-29-January-from-1-2pm?pg=2](https://www.mumsnet.com/Talk/mumsnet_live_events/2557552-Webchat-with-Professor-Siobhan-Quenby-on-recurrent-miscarriage-on-Friday-29-January-from-1-2pm?pg=2)