

Impact case study (REF3)

Institution: Imperial College London		
Unit of Assessment: 01 Clinical Medicine		
Title of case study: Setting the international standard for the diagnosis of miscarriage		
Period when the underpinning research was undertaken: 2010-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Tom Bourne	Clinical Professor in Gynaecology	2008 to present
Jessica Farren	Clinical Research Fellow	2014 - 2015
Shabnam Bobdiwala	Clinical Research Fellow	2015 - 2017
Period when the claimed impact occurred: 2014 - 2020		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact (indicative maximum 100 words)		
<p>Researchers at Imperial College demonstrated that existing ultrasound criteria used to diagnose miscarriage were unsafe, incorrectly diagnosed miscarriage in up to 8% of cases and resulted in healthy pregnancies being terminated.</p> <p>The subsequent formulation, validation and adoption of new diagnostic criteria has prevented termination of >1,200 healthy wanted pregnancies each year in the UK and resulted in a rapid revision of miscarriage guidelines across the world.</p> <p>Furthermore, parallel studies demonstrated that early pregnancy loss frequently resulted in post-traumatic stress leading directly to its inclusion in the National Bereavement Care Pathway and intense media interest highlighting the psychological consequences of miscarriage internationally.</p>		
2. Underpinning research (indicative maximum 500 words)		
<p>Accurate diagnosis of miscarriage in early pregnancy (i.e. up to 12 weeks' gestation) is of critical importance as an incorrect diagnosis may result in termination of a healthy pregnancy. Diagnosis is made difficult by the limitations of ultrasonography to visualise embryonic structures as well as uncertainties over the gestational age in many cases.</p> <p>At Imperial College between 2011 and 2015, Professor Tom Bourne conducted a prospective multi-centre observational study investigating the limitations of the existing definitions of miscarriage (1, 2). A total of 3,192 women were recruited from early pregnancy assessment units in seven hospitals: four university hospitals in London (St George's, Queen Charlotte's and Chelsea, St Thomas', and St Mary's), one university hospital outside London (Princess Anne, Southampton), and two London general hospitals with university affiliations (Chelsea and Westminster, and Northwick Park). This collaborative network was made possible by Imperial's strong national networks links as well as its clinical reputation.</p> <p>Data were collected in two phases. First, in an initial development study, 1,600 women were recruited consecutively between September 2010 and March 2011 at the four London university hospitals (1). Standardised ultrasound data relating to gestation sac and embryo size, as well as fetal growth, were collected at the initial scans and at follow up examinations. The results demonstrated that the cut-off values used to define miscarriage were unsafe.</p>		

This development study prompted a consensus meeting attended by Professor Bourne and subsequent publication of a review paper in the *New England Journal of Medicine*, which adopted the revised guidelines to diagnose miscarriage proposed by the Imperial group (2).

A follow-on study aimed to validate both the development study findings and the subsequent guideline changes by establishing the performance of the new miscarriage diagnostic criteria with high levels of certainty (3). Secondary aims were (a) to examine the influence of gestational age on interpretation of key measurements and (b) to determine the optimal intervals between scans and identify findings on repeat scans that definitively diagnose pregnancy failure.

The study validated the initial finding that the measurements of mean gestation sac diameter and embryo size used in earlier guidance were likely to lead to miscarriage being diagnosed in a significant number of healthy pregnancies (as many as 1 in 12 false positives) (3).

During these Imperial-led studies, the researchers became acutely aware of the frequent and severe psychological consequences of miscarriage. To address this, a pilot study, in which women were given validated questionnaires for depression, anxiety and post-traumatic stress disorder one and three months after an early pregnancy loss was undertaken. This demonstrated that as many as 38% of women suffered moderate to severe post-traumatic stress three months after an early pregnancy loss (4).

A subsequent study of 737 women given validated questionnaires three, six and nine months after an early pregnancy loss showed that at least 20% of women still had moderate to severe post-traumatic stress symptoms nine months after miscarriage or ectopic pregnancy (5). In October 2020 the group published complementary findings in 386 partners of women experiencing early pregnancy loss demonstrating that although less frequent 7% of partners had post-traumatic stress at one month, 8% at three months and 4% at nine months (6).

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

(1) Abdallah, Y., Daemen, A., Kirk, E., Pexsters, A., Najji, O., Stalder, C., Gould, D., Ahmed, S., Guha, S., Syed, S., Bottomley, C., Timmerman, D., Bourne, T. (2011). Limitations of current definitions of miscarriage using mean gestational sac diameter and crown-rump length measurements: a multicenter observational study. *Ultrasound Obstet Gynecol*; 38(5): 497-502. [DOI](#).

(2) Doubilet, P.M., Benson, C.B., Bourne, T., Blaivas, M. for the Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy. (2013). Diagnostic criteria for nonviable pregnancy early in the first trimester. *New England Journal of Medicine*; 369(15): 1443-51. [DOI](#).

(3) Preisler, J., Kopeika, J., Ismail, L., Vathanan, V., Farren, J., Abdallah, Y., Battacharjee, P., Van Holsbeke, C., Bottomley, C., Gould, D., Johnson, S., Stalder, C., Van Calster, B., Hamilton, J., Timmerman, D., Bourne, T. (2015). Defining safe criteria to diagnose miscarriage: prospective observational multicentre study. *BMJ*; 351: h4579. [DOI](#).

(4) Farren, J., Jalbrant, M., Ameye, L., Joash, K., Mitchell-Jones, N., Tapp, S., Timmerman, D., Bourne, T. (2016). Post-traumatic stress, anxiety and depression following miscarriage or ectopic pregnancy: a prospective cohort study. *BMJ Open*; 6(11): e011864. [DOI](#).

(5) Farren, J., Jalbrant, M., Falconieri, N., Mitchell-Jones, N., Bobdiwala, S., Al-Memar, M., Tapp, S., Van Calster, B., Wynants, L., Timmerman, D., Bourne, T. (2020). Post-traumatic stress, anxiety and depression following miscarriage and ectopic pregnancy: a multicenter, prospective, cohort study. *Am J Obstet Gynecol*; 222(4): 367.e1-367.e22. [DOI](#).

(6) Farren, J., Jalbrant, M., Falconieri, N., Mitchell-Jones, N., Bobdiwala, S., Al-Memar, M., Tapp, S., Van Calster, B., Wynants, L., Timmerman, D., Bourne, T. (2020). Differences in post-traumatic

stress, anxiety and depression following miscarriage or ectopic pregnancy between women and their partners: multicenter prospective cohort study. *Ultrasound Obstet Gynecol*; 57(1): 141-148. [DOI](#).

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

By demonstrating that the criteria used to diagnose miscarriage were unsafe, the initial development study conducted by Prof Bourne and colleagues in 2010/2011 prompted a consensus meeting attended by Prof Bourne in the United States. This meeting led directly to the publication of a review paper in the *New England Journal of Medicine* that used the Imperial data to propose new safe diagnostic criteria (research reference 1 above). The Royal College of Obstetrics and Gynaecology (RCOG) in the UK published an addendum to its guidance within a week of the initial development study being published following an urgent meeting of its ultrasound committee [A].

Data reported in the validation study published in the *BMJ* in 2015 enabled recommendations to be made on the follow up of women deemed at risk of a miscarriage, providing information on how long to wait before repeating ultrasound examinations and what to expect to see on those examinations.

Following the publication of the validation study in the *BMJ*, the American College of Obstetricians and Gynecologists published a practice bulletin in 2016 citing the Imperial-led research as the driver behind changing the diagnostic guidelines for miscarriage in the United States [B]. In 2018, the Australasian Society for Ultrasound in Medicine also published new guidelines for miscarriage diagnosis using the Imperial criteria [C]. In the same year, the American College of Radiology updated their guideline by adopting the updated criteria [D]. Now countries throughout the world, including France and Italy, have changed to the new criteria for miscarriage diagnosis based on the data generated by the Imperial College team [E, F]. These changes in guidance were prompted by Imperial data showing existing diagnostic criteria were unsafe and have resulted in the implementation of safer criteria based on the Imperial study.

Prior to these guideline changes, it is possible that thousands of wanted pregnancies throughout the world may have had surgical or medical treatment for a miscarriage based on a misdiagnosis. The data generated from the research at Imperial College has shown that, using the existing guidelines, the risk of a misdiagnosis using embryo size measurements and an apparent lack of a visible heartbeat on ultrasonography was at least 8% (just over 1 in 12), leading in many cases to unnecessary termination of a wanted pregnancy.

An American study suggested that for women presenting with a possible miscarriage, about 12% may have been given an incorrect diagnosis of miscarriage using the guidance that existed in the United States prior to the Imperial study [G]. Applying such calculations to the UK, as many as 1,200 healthy wanted pregnancies could have been terminated each year owing to an incorrect diagnosis of miscarriage.

Furthermore, the novel findings from the Imperial study investigating post-traumatic stress in women following early pregnancy loss attracted intense media interest and were presented at the "All Parliamentary Group on Baby Loss" in the House of Commons [H]. This work directly resulted in the inclusion of early pregnancy loss in the National Bereavement Care Pathway [I], an initiative that is dedicated to ensuring that bereaved parents are offered equal, high quality, individualised, safe and sensitive care in all hospitals in the UK.

The publication of the full paper in 2020 describing the psychological impact of miscarriage and ectopic pregnancy received one the biggest media coverage of any story from Imperial College and trended on social media in the UK. It was covered throughout the world, increasing awareness of the important long-term psychological consequences of ectopic pregnancy and miscarriage and enabling women to tell their stories. This was exemplified by two leading articles in the *Guardian*

in which readers described their experiences of the pain of miscarriage (>120,000 print subscribers > 350,000 digital subscribers) [J].

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

[A] RCOG guideline addendum - archived [here](#).

[B] American College of Obstetrics and Gynecologists Guidelines: <https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Bulletins/Committee-on-Practice-Bulletins-Gynecology/Early-Pregnancy-Loss-2016>. Archived [here](#).

[C] Australasian guidelines:

Mizia K, Westerway S, Robertson M, Parry E, Paoletti D, Perry D, Ramkrishna J, Macpherson L, Condous G. Guidelines for the performance of the first trimester ultrasound. *Australasian Journal of Ultrasound in Medicine*, 2018; 21 (3): 179-183. [DOI](#).

(REFERENCE 3 cites the full Imperial study in the BMJ: “If there is any doubt as to the diagnosis of a miscarriage, a further scan should be offered³)

[D] Brown DL, Packard A, Maturen KE, Deshmukh SP, Dudiak KM, Henrichsen TL, Meyer BJ, Poder L, Sadowski EA, Shipp TD, Simpson L, Weber TM, Zelop CM, Glanc P. American College of Radiology Appropriateness Criteria First Trimester Vaginal Bleeding. Expert Panel on Women’s Imaging; *J Am Coll Radiol*. 2018 May;15(5S): S69-S77. [DOI](#).

(REFERENCE 17 cites the NEJM consensus: This reference is cited 5 times on page S72 in relation to the importance of ultrasound measurement in the accurate diagnosis of miscarriage)

[E] Huchon C, Deffieux X, Beucher G, Capmas P, Carcopino X, Costedoat-Chalumeau N, Delabaere A, Gallot V, Iraola E, Lavoue V, Legendre G, Lejeune-Saada V, Leveque J, Nedellec S, Nizard J, Quibel T, Subtil D, Vialard F, Lemery D; Collège National des Gynécologues Obstétriciens Français. Pregnancy loss: French clinical practice guidelines. *Eur J Obstet Gynecol Reprod Biol*. 2016 Jun; 201:18-26. [DOI](#).

(REFERENCE 12 cites the NEJM consensus: “The viability of an intrauterine pregnancy is uncertain when the transvaginal ultrasound image shows a gestational sac <25 mm without an embryo or with an embryo <7 mm with no heartbeat [12]”).

[F] Italian Guidelines for diagnosing miscarriage - from the Società Italiana di Ecografia Ostetrica e Ginecologica e Metodologie Biofisiche, 2015, page 1. <https://www.sieog.it/wp-content/uploads/2016/02/Linee-Guida-2015-x-sito1.pdf>

(Cites the NEJM consensus). Archived [here](#).

[G] Hu M, Poder L, Filly RA. Impact of new society of radiologists in ultrasound early first-trimester diagnostic criteria for nonviable pregnancy. *J Ultrasound Med*, 2014 Sep;33(9):1585-8. [DOI](#).

(REFERENCE 11 cites the NEJM consensus: “Incorrect diagnosis of pregnancy failure can prompt interventions that interrupt a pregnancy that otherwise would have had a normal outcome. To minimize or avoid false-positive test results, more stringent diagnostic criteria for nonviability by expanding the crown-rump length cut-off to 7 mm for embryos without a heartbeat and the mean sac diameter cut-off to 25 mm for “empty” sacs was recently recommended by a Society of Radiologists in Ultrasound multispecialty consensus panel.¹¹).

[H] <https://www.lullabytrust.org.uk/wp-content/uploads/Minutes-APPG-on-Baby-Loss-14th-Dec-2016-1.pdf>. Archived [here](#).

(Prof. Bourne invited speaker)

[I] <https://nbcpathway.org.uk/pathways/miscarriage-bereavement-care-pathway> Full document page 34. Archived [here](#).

[J] <https://www.theguardian.com/lifeandstyle/2020/jan/15/pain-of-miscarriage-readers-share-experiences>) Archived [here](#).

(References Imperial Study)

<https://www.theguardian.com/society/2020/jan/15/share-your-experiences-of-how-early-miscarriage-impacted-on-your-mental-health> (archived [here](#)) **(References Imperial Study)**