

Institution: Keele University
Unit of Assessment: UoA 3
Title of case study: Disorders of the Menstrual Cycle – the Menstrual Pictogram
1. Summary of the impact <p>Research by Prof Shaughn O'Brien and his team at Keele has led the field in the quantification of symptoms and treatment of disorders of the menstrual cycle. Examples include the Menstrual Pictogram, designed to quantify menstrual blood loss, development of digital devices to measure menstrual symptoms and key systematic reviews of the treatment of premenstrual syndrome. Impact includes substantial improvement in the acceptability to women in the methods of symptom measurement, academic and commercial impact due to validation of treatment interventions, including requirements for regulatory purposes and the development of international consensus statements and evidence-based guidelines for management of disorders of the menstrual cycle.</p>
2. Underpinning research <p><u>Quantifying menstrual blood loss – the Menstrual Pictogram.</u></p> <p>The original prototype, a pictorial blood loss assessment chart (PBAC), designed to quantify menstrual blood loss was devised by Prof O'Brien (1990) as a symptom score for use in research trials and FDA submissions for drug licensing. To improve its accuracy and efficacy the team went on to devise the Menstrual Pictogram with the specific aim of measuring menstrual blood loss in millilitres and validating it against the gold standard alkaline haematin method and attempt to completely replace the cumbersome alkaline haematin (AH) method [1].</p> <p>Over time, with the evolution of sanitary products the Pictogram became inaccurate due to their use of superabsorbent polymers (SAP) (lighter and very absorbent). The availability of these more refined sanitary products thus made the original Menstrual Pictogram less acceptable to women. If use of pictograms was to continue it became necessary to develop menstrual pictograms containing SAP. To achieve this, Keele University Department of Obstetrics and Gynaecology has developed a scientific collaboration with Bayer HealthCare to develop an updated pictorial method (Menstrual Pictogram) for assessing the volume of menstrual blood loss using sanitary wear containing superabsorbent polymers [2,3]. The team undertook full patient interpretation studies, in-house and laboratory evaluation and clinical validation to develop this definitive Pictogram (see section 4, collaborative publication in press). The culmination of this work which is now completed is under consideration by drug regulatory authorities in USA, Europe and Japan as a replacement method for the original pictogram for use in clinical trials.</p> <p><u>Measuring symptoms of the menstrual cycle: Symptometrics</u></p> <p>In parallel with the development of the pictogram, the team has combined this with quantification methods for Menstrual Pain and Premenstrual Syndrome that is suitable for hand held computer-based methods (personal digital assistants, PDAs), so integrating the measurement of all menstrual cycle symptoms. This was published as menstrual Symptometrics in 2002 [4] and has since been updated and refined. The pace of technological change and new generations of PDAs has necessitated development of an internet-based version, www.symptometrics.com that can interface with PCs, mobile phones, iPads etc. Developed for patient and GPs to use this award winning technology has the capacity to feed back results and even produce a diagnostic report (see section 4).</p> <p><u>Literature reviews of the management of Premenstrual Syndrome</u></p> <p>The Keele group has undertaken important systematic reviews on SSRIs, GnRH analogues, Oestrogen and Progestogens in the treatment of premenstrual syndrome. These include evaluation</p>

Impact case study (REF3b)

of the efficacy of serotonin inhibitors in the treatment of symptoms, initially published in the *Lancet* [5] but subsequently updated as a *Cochrane* review [6]. Their review showing the lack of efficacy of progesterone/progestagens in this condition, published in *BMJ* [7], refuted a long-held view that these are effective.

3. References to the research

1. Wyatt KM, Dimmock PW, Walker TJ and O'Brien PMS (2001) Determination of total menstrual blood loss. *Fertility and Sterility* 76 (1): 125 – 131
2. Magnay JL, Nevatte TM, Dhingra V, O'Brien PMS 2010 Menstrual blood loss measurement: validation of the alkaline haematin technique for feminine hygiene products containing superabsorbent polymers. *Ferti.Steril* 94(7):2742-6.
3. Magnay JL, Schönicke G, Nevatte TM, O'Brien S, Junge W (2011) Validation of a rapid alkaline hematin technique to measure menstrual blood loss on feminine towels containing superabsorbent polymers. *Fertility and Sterility*. 96(2): 394-398
4. Wyatt K, Dimmock P, Hayes Gill B, Crowe J, Francon B and O'Brien PMS (2002) Menstrual Symptometrics: a simple computer-aided method to quantify menstrual cycle disorders. *Fertility and Sterility* 78(1): 96-101
5. Dimmock P, Wyatt K, Jones P and O'Brien PMS (2000) Efficacy of selective serotonin reuptake inhibitors in premenstrual syndrome: a systematic review. *Lancet* 2000; 356:1131-36
6. Marjoribanks J, Brown J, O'Brien PM, Wyatt K. 2013 Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst Rev.* (2013) Jun 7;6:CD001396. doi: **10.1002/14651858.CD001396.pub3**
7. Wyatt K, Dimmock P Jones P and O'Brien PMS (2001) A systematic review to assess the efficacy of progesterone/progestagens in the treatment of premenstrual syndrome. *BMJ* 323: 776-80

Relevant Grants:

Awarded to	Title	Sponsor	Duration	Value
O'Brien & Nevatte	Symptometrics for Quantification of Disorders of Menstrual Cycle	Advantage West Midlands	2009 -10	£30K
O'Brien	Consensus meeting	Bayer	2007	£80K
O'Brien	Luteal Fluoxetine in PMS	Lilly Pharmaceutical	2000-03	£210,000
O'Brien	Validation of a new menstrual pictogram (SAP-c version) for use with ultra-slim towels that contain superabsorbent polymers	BayerHealthCare	2005-13	£600,000

4. Details of the impact

Menstrual Pictogram:

Direct impact: The immediate impact of the menstrual pictogram has been to provide a simple, inexpensive, validated tool to replace cumbersome collection of sanitary wear. It provides a quantitative means of assessment and diagnosis of heavy menstrual bleeding that is infinitely more acceptable to women and researchers in the field. It has been externally validated for diagnostic purposes [1] and used by researchers at various stages of its development to evaluate the impact of interventions to treat heavy menstrual blood loss in high profile clinical trials [2,3].

Impact on the pharmaceutical industry:

Heavy menstrual bleeding (HMB) associated with fibroids affects up to 1 in 4 women and the development of safe drugs that can avoid the use of hysterectomy to treat this condition is both a

Impact case study (REF3b)

high clinical priority and an important market for the pharmaceutical industry. The first menstrual pictogram (PBAC) has been used (e.g. by American Pharma) for key studies of HMB, e.g. **PEARL II**, to support the successful licensing applications for new drugs such as the progesterone receptor modulator, Ulipristal, to obtain FDA approval [3]. Recent refinement of the pictogram to account for the superabsorbent polymer sanitary materials will be evaluated for international regulatory approval by FDA, EMA, and PDMA (Japan) [4].

Symptometrics.

Symptometrics.com, the world's first internet-based premenstrual syndrome symptom quantification technique (see Section 2) has received two awards for medical technical innovation – the ICT West Midlands National Excellence Award – Knowledge Transfer 2010, and the Medilink WM Medical and Healthcare Business Awards 2010, [5].

Wider impact:

The research at Keele has advanced current thinking and clinical management of disorders of the menstrual cycle, particularly premenstrual disorders and heavy menstrual bleeding. This research has underpinned the development of evidence based guidelines [6] and state of the art reviews of the management of menstrual disorders [7]. Professor O'Brien's pre-eminence in the field has enabled him to establish the International Society for Premenstrual Disorders (ISPM), which he currently chairs. This organisation is formulating a series of high impact International Expert Consensus Statements; the first of these, published in 2011 focussed on the diagnosis, classification, quantification, clinical trial design and management of premenstrual syndrome [8] precipitating editorials in high impact journals (e.g. *BMJ*, [9]). Professor O'Brien was Vice President of the Royal College of Obstetricians and Gynaecologists a role in which he was responsible for national professional and clinical standards with oversight of the development of numerous clinical guidelines including that for PMS (although these were independently authored) [6]. Additional impact underpinned by research at Keele is the work of the British Society of Psychosomatic Obstetrics and Gynaecology, (O'Brien currently chair), a multidisciplinary specialist society which leads the biopsychosocial aspects obstetrics and gynaecology nationally [10].

5. Sources to corroborate the impact

1. *External validation of use of the Menstrual Pictogram to evaluate menstrual blood loss by Abbott Laboratories, USA:*

Larsen L, Coyne K, Chwalisz K. Validation of the menstrual pictogram in women with leiomyomata associated with heavy menstrual bleeding. *Reprod Sci.* 2013 Jun;20(6):680-7.

doi: 10.1177/1933719112463252

2. *Example of use of the menstrual pictogram to evaluate the effects of an intervention (asoprisnil) on uterine blood loss:* Wilkens J, Chwalisz K, Han C, Walker J, Cameron IT, Ingamells S, Lawrence AC, Lumsden MA, Hapangama D, Williams AR, Critchley HO. Effects of the selective progesterone receptor modulator asoprisnil on uterine artery blood flow, ovarian activity, and clinical symptoms in patients with uterine leiomyomata scheduled for hysterectomy. *J Clin Endocrinol Metab.* 2008 93(12):4664-71. **doi:10.1210/jc.2008-11043.**

3. *One of the key studies designed to obtain regulatory approval for the use of Ulipristal for the treatment of uterine fibroids used the pictogram method:* Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuk B, Baró F, Nouri K, Selvaggi L, Sodowski K, Bestel E, Terrill P, Osterloh I, Loumaye E; PEARL II Study Group. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med.* 2012 Feb 2;366(5):421-32. **doi: 10.1056/NEJMoa11031804**

4. *Evidence to corroborate collaborative research and use of this research to submit to international regulatory bodies the modified pictogram:* please contact, Bayer HealthCare Global Clinical Development Leader, Berlin, Germany. See also publication of the latest version of the pictogram:

Impact case study (REF3b)

Magnay JL, Nevatte TM, O'Brien S, Gerlinger C, Seitz C (2013) Validation of a new menstrual pictogram (SAP-c version) for use with ultra-slim towels that contain superabsorbent polymers. *Fertility and Sterility*, in press.

5. *Award winning technology*: see www.symptometrics.com to access details of the ICT Excellence Award for Knowledge Transfer, sponsored by the University of Warwick Science Park, at the 2010 awards in Birmingham, and the Medilink West Midlands start-up award.

6. *Guidelines for Premenstrual Syndrome*:

O'Brien PMS Edited (not authored) (2007) Green-Top Guideline No. 48 Management of Premenstrual Syndrome (Commissioned, Overseen and Edited as Chairman of Standards Committee, Royal College of Obstetricians and Gynaecologists).

7. *State of the art review of Premenstrual Syndrome*:

Yonkers K, O'Brien PMS and Eriksson E (2008) Update on the Pathophysiology and Treatment of Premenstrual Syndrome. *Lancet* 371: 1200-10

8. *International consensus statement for premenstrual disorders*:

O'Brien PMS, Bäckström T, Brown C, Dennerstein L, Endicott J, Epperson CN, Eriksson E, Freeman E, Halbreich U, Ismail KM, Panay N, Pearlstein T, Rapkin A, Reid R, Schmidt P, Steiner M, Studd J, Yonkers K. 2011 Towards a consensus on diagnostic criteria, measurement and trial design of the premenstrual disorders: the ISPMD Montreal consensus. *Arch Women's Ment Health*. (1) :13-21. 2011

9 For BMJ commentary on the ISPMD consensus statement see: *BMJ* 2011;342:d2994
doi.org/10.1136/bmj.d2994

10. *Website of the British Society of Psychosomatic Obstetrics, Gynaecology and Andrology*:
<http://www.bspoga.org/>