Institution: University of Birmingham

Unit of Assessment: 2 – Public Health, Health Services and Primary Care

Title of case study: Establishing a hormone-releasing coil as the first-line treatment for women with heavy periods

Period when the underpinning research was undertaken: 2004-2020

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:
Prof. Janesh Gupta	Professor of Obstetrics and Gynaecology	1998-present
Prof. Joseph Kai	Senior Lecturer	1998-2002
Dr. Helen Pattison	Senior Lecturer	1996-2003
Prof. Richard Lilford	Professor of Public Health	2019-present
	Honorary Professor of Public Health	2015-present
	Head of School (Health and Population Sciences)	2005-2009
Prof. Tracy Roberts	Professor of Health Economics	2009-present
	Senior Lecturer in Health Economics	1998-2009
Dr. Jane Daniels	Honorary Reader	2017-2020
	Reader in Women's Health & Trial Coordinator	2006-2017
Prof. Richard Gray	Honorary Senior Research Fellow	2010-2020
	Professor of Medical Statistics	1996-2010

Period when the claimed impact occurred: 2014 – July 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Heavy menstrual bleeding (HMB) is a common condition that significantly compromises the quality of life of women worldwide. Work from the University of Birmingham assessing the benefit of fitting a simple hormone-releasing intrauterine coil, termed the levonorgestrel-releasing intrauterine system coil (LNG-IUS), has improved care for women suffering with HMB.

Specifically we have:

(i) Improved the physical and psychological health, and well-being of women.

(ii) Changed national and international clinical guidelines in the UK, Australia and USA which now define LNG-IUS as the first-line treatment.

(iii) Changed clinical practice as LNG-IUS becomes the first-line treatment for HMB.

(iv) Reduced healthcare costs as medical management options for HMB are four-to-five-fold cheaper than hysterectomy.

2. Underpinning research

Heavy menstrual bleeding (HMB) is a common condition that significantly compromises the emotional and physical well-being of women worldwide, having a negative impact on their personal, social and working routine. HMB also places a significant burden on healthcare systems. In the UK, 1 in 20 women aged between 30–49 years (400,000 women) consult their GP each year for menstrual disorders, of which HMB is the most common, and menstrual disorders account for 12% of all referrals to UK gynaecology services.

Several oral hormonal and non-hormonal medical treatments are available to treat HMB but are associated with systemic effects. Hysterectomy, surgical removal of the womb, is also an option but makes the patient infertile, has a long post-operative recovery period and can lead to postoperative complications including pain, infection, scarring and increased susceptibility to osteoporosis.

The side-effects of medical therapy might be reduced, and efficacy increased, by local delivery using intrauterine devices. The levonorgestrel-releasing intrauterine system coil (LNG-IUS) is a T-shaped plastic device that is fitted in the womb to deliver a continuous low dose of local levonorgestrel (progestogen) for up to five years. However, until the work of Gupta, it was unclear if (1) LNG-IUS was the optimum first-line medical treatment for HMB or (2) if the benefits persisted beyond the short term.

To establish the **clinical effectiveness and economic benefit of LNG-IUS** compared with standard oral medications for the management of HMB in a primary care setting, Gupta designed and led the multicentre randomised controlled trial, **ECLIPSE** (Effectiveness and Cost-effectiveness of Levonorgestrel-Containing Intrauterine System in Primary Care against Standard TrEatment for Menorrhagia).

ECLIPSE was the **largest ever clinical trial conducted to assess medical management in HMB** and was undertaken in 63 centres. Over 570 women were recruited between February 2005 and July 2009, randomised to receive either LNG-IUS or usual medical treatment and followed up at two [R1] and five [R2, R3] years to assess the effects of treatment on women's quality of daily life, which encompassed family life and relationships, physical health, work and daily routine, practical difficulties, psychological health and social life. The research delivered the following key findings (KF):

- **KF1:** Both LNG-IUS and standard oral treatments improve the quality of life of women with HMB. [R1]
- **KF2:** LNG-IUS significantly improves the quality of life of women with HMB compared to standard oral medications and this continues for over 5 years. [R1, R2, R3]
- **KF3:** Women with LNG-IUS are less likely to change from their assigned therapy. (68% of the LNG-IUS group were still on assigned therapy at 2 years vs 38% for standard oral medication and this difference persisted at 5 years (47% LNG-IUS vs 15% standard oral medication). [R1, R3]
- **KF4:** LNG-IUS and standard oral medications have equally high surgery-free survival at 5 years (80% LNG-IUS vs 77% standard oral medication). [R2, R3]
- **KF5:** LNG-IUS is a more cost-effective treatment for HMB than standard oral medications and fulfils National Institute for Health and Care Excellence (NICE) cost-effectiveness guidelines for recommendation into clinical practice in the UK. [R2, R4]

3. References to the research

R1. Gupta J, Kai J, Middleton L, Pattison H, Gray R, Daniels JP. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. N Engl J Med 2013; 368: 128-37 (up to 2 year follow up). doi: 10.1056/NEJMoa1204724

R2. Gupta JK, Daniels JP, Middleton LJ, Pattison HM, Prileszky G, Roberts TE, Sanghera S, Barton P, Gray R, Kai J (2015). A randomised controlled trial of the clinical effectiveness and cost-effectiveness of the levonorgestrel-releasing intrauterine system in primary care against standard treatment for menorrhagia: the ECLIPSE trial. Health Technol Assess: 19(88): 1-118. doi: 10.3310/hta19880.

R3. Kai J, Middleton L, Daniels J, Pattison H, Tryposkiadis K, Gupta J; ECLIPSE trial collaborative group (2016). Usual medical treatments or levonorgestrel-IUS for women with heavy menstrual bleeding: long-term randomised pragmatic trial in primary care. Br J Gen Pract: 66(653): e861-e870 (5-year follow-up). doi: 10.3399/bjgp16X687577

R4. Sanghera S, Roberts TE, Barton P, Frew E, Daniels J, Middleton L, Gennard L, Kai J, Gupta JK. Levonorgestrel-releasing intrauterine system vs. usual medical treatment for menorrhagia: an economic evaluation alongside a randomised controlled trial. PLoS One 2014; 9(3): e91891. doi: 10.1371/journal.pone.0091891

4. Details of the impact

We have **improved the management of HMB**, a debilitating condition that compromises the quality of daily life for many women. With LNG-IUS, women with HMB **experience improved quality of daily life** both physically and psychologically compared with those taking standard systemic medication. Women who have this treatment experience less disruption to their daily routine, their work and their social life. Furthermore, only 20% of patients proceed to hysterectomy, which removes fertility and can lead to multiple other morbidities [R1–R3]. A recent study of women's views toward treatment for HMB attests that women are "thrilled on learning that the [LNG-IUS] […] put there for five years […] could help [their] condition" [S1, participant 15]. Specifically, we have **changed guidelines** and **changed clinical practice** in the following ways.

1. Clinical guidelines have changed for the management of HMB

(i) UK clinical guidelines and recommendations have changed to adopt the treatment LNG-IUS for HMB.

The UK National Institute for Health and Care Excellence (NICE) clinical guidelines for the management of HMB were updated in March 2018. A key change is recommendation 1.5.2 which advises (based on [R2]) to "**consider an LNG-IUS as the first treatment for HMB** in women with no identified pathology or fibroids less than 3 cm in diameter […]" [S2, p. 11]. This represents a **step change in the rationale and certainty of the UK clinical practice guideline**; the previous 2007 guideline listed LNG-IUS as a treatment to "consider" for HMB when either hormonal or non-hormonal treatments are acceptable [S3, p. 8]. The systematic review that advised the recommendation found that "alternative drugs (NSAIDs, tranexamic acid and combined oral contraceptives) were no better than LNG-IUS in terms of effectiveness" [S3, p. 66]. At the time, NICE indicated that this might need revising: referring to our ECLIPSE trial that was in progress they stated, "the direct comparison data comparing LNG-IUS with other pharmaceutical treatments may prove useful for determining the place of LNG-IUS in the treatment of HMB" [S3, p. 56]. Accordingly, to inform the 2018 update, NICE commissioned another review on treatment for HMB [S4i]. Five 'High quality' Cochrane systematic reviews, including Lethaby 2015 [S4ii] and 18 additional publications, including R2, contributed evidence [S4i, p. 11]. R1 was one of only seven studies comparing LNG-IUS with medical treatments that informed S4ii [S4ii, p. 16] and of these it was the only study described as a "large good-quality pragmatic trial" [S4ii, p. 19]. Heavily underpinned by our findings, the 2018 review [S4i] agreed with S3 that LNG-IUS should be the first treatment for HMB for health economic reasons — "offering the best balance of benefits and costs" [S2, p. 22-23, S4i]. It also added further rationale for **defining LNG-IUS the first-line treatment through providing evidence of clinical effectiveness** including "improved health-related quality of life [KF2] and satisfaction with treatment" [S2, p. 22-23, S4i; KF3].

In the 2018 guideline update, NICE explicitly recommended that **LNG-IUS should be prescribed in preference to other drugs by**:
(1) Describing it as the "first treatment";
(2) Isolating it from the other drugs which are listed separately in recommendation 1.5.3;
(3) Removing order of consideration from among the other drugs, and
(4) Making offering the alternative drugs conditional upon the woman either declining an LNG-IUS or being unsuitable.

To aid clinician uptake of their recommendations, NICE featured their guidance on the use of LNG-IUS in the June 2018 issue of their monthly prescribing bulletin 'NICE Bites' [S5].

(ii) Internationally clinical guidelines and recommendations have changed to adopt the treatment LNG-IUS for HMB.

Specifically:

- In the USA, the 2015 **American College of Obstetricians and Gynaecologists (ACOG)** gynaecology expert review on the medical management of abnormal uterine bleeding in reproductive-aged women concluded LNG-IUS has "high efficacy" for treatment of abnormal uterine bleeding and lists LNG-IUS first among eight therapies for HMB without underlying systemic cause. It states that "in women with HMB, quality of life is improved remarkably when the LNG-IUS is used" [S6i; R1].
- In Canada, the 2016 **Ontario Health Technology Assessment Series**, said that "The LNG-IUS works well and costs less compared with other options to treat heavy menstrual bleeding […] Funding the LNG-IUS to treat heavy menstrual bleeding would result in cost savings to the Ontario health care system" [S6ii; R1, R2].
- In Australasia, **The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)** said in 2018 "the most effective hormone method is the intrauterine device (LNG-IUS)" [S6iii; KF2].
- In New Zealand, University of Auckland Professor of Obstetrics and Gynaecology and Co-ordinating Editor of Cochrane Gynaecology and Fertility said: "The mainstay of treatment [for women with HMB] used to be hysterectomy. With the introduction of the LNG-IUS device there are now several other options [besides hysterectomy] for women with HMB" [S6iv; R1].

2. Clinical practice for the management of HMB has changed.

We have **changed clinical practice** across the UK. **NHS Clinical Commissioning Groups (CCGs) and Trusts revised the guidelines in their policy statements** on the use of hysterectomy for HMB following our findings [S2; KF1, KF2] so that **hysterectomy for HMB would only be funded if several criteria were met, including the trial of an intrauterine system or LNG-IUS for at least six months** (unless contraindicated or declined by the patient) [S7].

A National Institute for Health Research (NIHR) **'Signal' report** [S8], accompanied by an expert commentary from Gupta, assisted the making of these decisions by communicating to the public and policy makers the message that "The LNG-IUS is more effective than oral medication as a treatment for HMB" [S4ii, S8; KF2]. The guidance was made **nationwide policy for clinical practice** when the **NHS released a verifying statement** in November 2018 directing all CCGs across England to follow the latest NICE guidance for HMB assessment and management [S2] and only consider hysterectomy when "other treatment options have failed; are contradicted; there is a wish for amenorrhoea (no periods); the woman (who has been fully informed) requests it; the woman no longer wishes to retain her uterus and fertility" [S9, p. 30].

Implementation of this change to practice has important **economic benefit by reducing treatment costs** as LNG-IUS and other medications are four-to-five-fold lower in cost than hysterectomy [R4]. As evidence of **uptake into practice** a statement from the Royal College of General Practitioners (RCGP) has confirmed that "GPs across the country are using these treatments [i.e. LNG-IUS] within primary care" and the clinical policy lead herself reported having

"fitted 45 LNG-IUS over the last year, even continuing through the pandemic" [S10]. In New Zealand, the LNG-IUS is now under government-subsidised funding, so is free in that country [S1].

5. Sources to corroborate the impact

S1: Henry C, Jefferies R, Ekeroma A, et al. Beyond the numbers—understanding women's experiences of accessing care for abnormal uterine bleeding (AUB): a qualitative study. BMJ Open 2020;**10:**e041853. doi: 10.1136/bmjopen-2020-041853. Available from: Study of women's experiences of care for AUB.
S2: NICE Heavy menstrual bleeding: assessment and management (NG88). 2018. Available from: NICE 2018 guideline NG88 on HMB.
S3: NICE Heavy menstrual bleeding clinical guideline. 2007. Available from: NICE 2007 guideline CG44 on HMB
S4i: Evidence reviews for management of heavy menstrual bleeding. NICE guideline 88 Evidence reviews. Available from: Evidence review for NICE 2018 guideline NG88 on HMB.
S4ii: Lethaby, A., et al., Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database Syst Rev, 2015(4): p. CD002126. doi: 10.1002/14651858.CD002126.pub3. Available from: Cochrane systematic review of progesterone or progestogen-releasing intrauterine systems for HMB
S5: A summary of prescribing recommendations from NICE guidance - HMB. 2018. Available from: NICE Bite No106 2018 on HMB.
S6: Collection of international clinical guidelines and recommendations that advise use of LNG-IUS to treat HMB.
S6i: American College of Obstetricians and Gynaecologists (ACOG) expert review on the medical management of abnormal uterine bleeding (AUB) in reproductive-aged women (2015).
S6ii: Ontario Health Technology Assessment Series. Levonorgestrol-Releasing Intrauterine System (52mg) for idiopathic Heavy Menstrual Bleeding: A Health Technology Assessment. Available from: Ontario 2016 recommendation of LNG-IUS for HMB.
S6iii: RANZCOG. Heavy Menstrual Bleeding. 2018. Available from: RANZCOG 2018 information resources on HMB.
S6iv: Farquhar C. Evidence-based medicine - the promise, the reality. Aust N Z J Obstet Gynaecol. 2018 Feb;58(1):17-21. doi: 10.1111/ajo.12768. Available from: Editorial covering treatments for HMB.
S7: Clinical Commisioning Group policy statements on the management of HMB.
S8: NIHR Signal Report: A hormone-releasing coil is best for relieving heavy periods. Available from: NIHR signal report 2015 on the hormone-releasing coil for relieving heavy periods.
S9: NHS directive: Evidence-Based Interventions: Guidance for CCGs. Available from: NHS guidance for CCGS.
S10: Statement on behalf of clinical policy lead for RCGP supporting use of LNG-IUS in primary care.