Institution: University of Birmingham

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Improving treatment for women suffering from Endometrial Hyperplasia

Period when the underpinning research was undertaken: 1998 – 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:
Professor Janesh Gupta	Professor of Obstetrics and Gynaecology	1998 – present
Dr Ioannis Gallos	Academic Clinical Lecturer in Obstetrics and Gynaecology;	2013 – 2016;
	Honorary Clinical Lecturer;	2018 – 2019;
	Senior Lecturer in Global Maternal Health	2018 – present

Period when the claimed impact occurred: August 2013 – December 2020

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

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

Our work has directly changed the first-line treatment for women with non-atypical endometrial hyperplasia (EH). Previously, this was operative hysterectomy whereas our work has shown excellent outcomes with the use of a progestogen-releasing coil (LNG-IUS) inserted into the womb.

As a result we have:

(i) **Improved patient health and well-being**, as fewer women now suffer fertility loss and the complications associated with hysterectomy, whilst benefiting from reduced risk of endometrial cancer;

(ii) **Changed UK and international guidelines** for the management of EH;

(iii) **Changed clinical practice in EH** management by >90% of UK gynaecologists.

2. Underpinning research (indicative maximum 500 words)

Endometrial carcinoma (EC) (cancer of the womb) is the most common gynaecological cancer in the western world. Globally, 199,000 new cases are diagnosed each year, including 9,300 in the UK. **Endometrial hyperplasia (EH)**, which is thickening of the womb lining due to increased abnormal cell division, can lead to EC if not treated.

The risk of developing EC is up to 40% for women with **atypical EH** (grossly abnormal cells on microscopy). However, 70% of women present with **non-atypical EH** (early abnormal changes to cells on microscopy), and this has only a 5% risk of EC. Despite this, the traditional first-line treatment for all types of EH has been hysterectomy (surgical removal of the womb).

In light of this, there has been concern that the risks of hysterectomy (which can include loss of fertility, pain, long postoperative recovery, scarring and increased susceptibility to osteoporosis) are not warranted in patients with non-atypical EH given the relatively low risk of EC. Furthermore, there is also the significant resource burden on the NHS with each operation costing approximately £5,000.

EH is driven by an imbalance of the hormones oestrogen and progesterone. Medical management using progestogens has been available since the 1950s and used for women where surgery was not possible. However, **whether progestogen therapy could provide a suitable first-line alternative to hysterectomy for non-atypical EH was not known**.

Between August 1998 and December 2010, Professor Janesh Gupta, at the University of Birmingham (UoB), collected a prospective database of endometrial biopsies (small pieces of tissue taken from the womb lining) from 344 women with EH attending the gynaecology department at the Birmingham Women's Hospital and who were treated with progestogens. This allowed his team to evaluate the efficacy of managing EH with either:

- The levonorgestrel-releasing intrauterine system coil (**LNG-IUS**) delivering progestogens directly into the womb at a continuous low dose over a 5-year period *or*
- A short course of **oral progestogens** (average 6 months, range 3–12 months)**.**

The women were monitored with regular follow-up biopsies and the longest follow-up now exceeds 15 years [R1, R2, R3, R4]. This cohort represents the largest and longest prospective study of patients with EH in the world. Gupta's research confirmed the following key findings (KF):

- **KF1:** Regression (return to normal) of EH occurs within 1 year of starting progestogen therapy for most women [R1] and is higher with LNG-IUS compared to oral progestogens (95% vs 84%) [R3, R4]. This is true for both non-atypical (97% vs 90%) and atypical EH (76% vs 46%) [R3, R4].
- **KF2:** Risk of relapse after initial regression is lower with LNG-IUS compared to oral progestogens (13% vs 28%) [R2, R4].
- **KF3:** Obesity (Body Mass Index ≥35) is strongly associated with failure to regress and with relapse following LNG-IUS treatment [R4].

Gupta and colleagues also conducted two systematic reviews between 2010 and 2012 to assess the overall evidence to support LNG-IUS as the first-line therapy for EH [R5] and progestogen therapy as an option for women with atypical EH or low grade EC who wish to preserve their fertility or who are not suitable for surgery [R6]. These reviews confirmed KF1 [R5] and also showed:

- **KF4:** Progestogen therapy can induce regression and/or delay progression of disease in women with atypical EH or EC, enabling women to have a child before needing surgery [R6].

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

R1. Varma R, Soneja H, Bhatia K, Ganesan R, Rollason T, Clark TJ, Gupta JK. The effectiveness of a levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of endometrial hyperplasia - a long-term follow-up study. Eur J Obstet Gynecol Reprod Biol 2008; 139(2): 169-75. doi: 10.1016/j.ejogrb.2008.02.022

R2. Gallos ID, Krishan P, Shehmar MS, Ganesan R, Gupta JK. Relapse of endometrial hyperplasia after conservative treatment: A cohort study with long term follow up. Hum Reprod 2013: 28(5): 1231-6. doi: 10.1093/humrep/det049

R3. Gallos ID, Krishan P, Shehmar M, Ganesan R, Gupta JK. LNG-IUS (Mirena®) versus oral progestogens treatment for endometrial hyperplasia: A long-term comparative cohort study. Hum Reprod 2013: 28(11): 2966-71. doi: 10.1093/humrep/det320

R4. Gallos ID, Ganesan R, Gupta JK. Prediction of regression and relapse of endometrial hyperplasia with conservative therapy. Obstet Gynecol 2013; 121: 1165-71. doi: 10.1097/AOG.0b013e31828cb563

R5. Gallos ID, Shehmar M, Thangaratinam S, Papapostolou TK, Coomarasamy A, Gupta JK. Oral progestogens vs levonorgestrel-releasing intrauterine system for endometrial hyperplasia: a systematic review and meta-analysis. Am J Obstet Gynecol 2010; 203: 547.e1-10. doi: 10.1016/j.ajog.2010.07.037

R6. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and meta-analysis. Am J Obstet Gynecol 2012; 207(4): 266e1-12. doi: 10.1016/j.ajog.2012.08.011

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

1. **Improved the health and well-being of women with non-atypical endometrial hyperplasia**

First-line **treatment in non-atypical EH is no longer invasive, debilitating and expensive surgery (hysterectomy), but a simple and effective hormone coil (LNG-IUS).** Furthermore, women who decline LNG-IUS can be offered oral progestogens instead. Both options preserve fertility and provide a high (>90%) chance of disease regression [KF1].

Reflecting the favourable change this has been for women, the **proportion of women accepting treatment at initial diagnosis has increased from 71% to 96%** in this REF period with progestogen therapy accounting for 88% of this change (68% LNG-IUS; 20% oral progestogens). This is evidenced by an analysis of the UK national histopathology database for non-atypical EH which showed that **50% of women diagnosed with non-atypical EH** between March 2017 and October 2020 **received LNG-IUS as their first treatment compared with 33%** of women diagnosed between March 2013 and February 2016. The proportions of women receiving **oral progestogens increased from 20% to 25%** in the same periods, and women opting for **no treatment at diagnosis fell from 29% to 4%** [S1].

Improved well-being is further supported by patients' accounts. For example, one patient said: "nothing could have been worse than having a cancer on top of all my other medical problems and therefore **it has been a life saver** to have 2 small devices fitted inside my womb that have prevented the risk of potentially developing cancer of my womb" [S2].

2. **Changed clinical guidelines in the UK and internationally**

We have changed clinical guidelines in EH with regard to: 1) treatment of non-atypical EH and 2) management of EC and atypical EH to prolong fertility:

2.1. Guidelines have changed in the UK and Hong Kong to **recommend progestogen-releasing device LNG-IUS therapy as the first-line treatment**, rather than hysterectomy, for non-atypical EH. Specifically:

- **UK 'Green Top' Guidelines** (2016) for the management of EH have changed [S3]. These guidelines, jointly produced by **the Royal College of Obstetricians and Gynaecologists (RCOG) and the British Society for Gynaecological Endoscopy (BSGE)**, state that: "Hysterectomy should not be considered as a first-line treatment for hyperplasia without atypia" and instead advise progestogen therapy because it "induces histological and symptomatic remission in the majority of women and avoids the morbidity associated with major surgery."
- Of the alternative progestogen therapies, they recommend that "The LNG-IUS should be the first-line medical treatment" because, compared with oral progestogens, "it has a higher disease regression rate with a more favourable bleeding profile and it is associated with fewer adverse effects." Furthermore, they advise to "retain the LNG-IUS for up to 5 years as this reduces risk of relapse." For women who decline the LNG-IUS, they recommend that "continuous progestogens should be used" [S3, p.3; R2–R5].

- **The Hong Kong College of Obstetricians and Gynaecologists** advised in 2015 that "hysterectomy should be considered [for the management of EH] if there is no response after insertion of LNG-IUS for a year" [S4, section 4.4; R1].

2.2. UK and international clinical guidelines for the management of EC and atypical EH have changed to recommend that **conservative progestogen-based therapies (LNG-IUS or oral progestogens) may be used in order to prolong fertility for selected cases of women with these conditions** [R6]. Specifically:

- In the UK, the 2017 **British Gynaecological Cancer Society (BGCS) guidelines** for practice in uterine cancer advised that "conservative management of endometrial cancer may be safe in the short term in selected women with grade 1 endometrial cancer and with superficial myometrial invasion" but recommended that hysterectomy should be considered after successful pregnancy, particularly if predisposing factors persist such as obesity or diabetes" [S5 section 11; R6].

- In 2019, **the American College of Obstetricians and Gynaecologists** (ACOG) reaffirmed the opinion first given in 2015 based on our work that "Systemic or local progestin therapy may be appropriate for women who are poor surgical candidates or who desire to retain fertility" [S6, p.5; R6].

- At the Consensus Conference on Endometrial Cancer in 2016, **European cancer societies** including the European Society for Medical Oncology (ESMO), the European Society of Gynaecological Oncology (ESGO) and the European Society for Radiotherapy and Oncology (ESTRO) gave the collective guidance that "Maintenance treatment should be considered in responders who wish to delay pregnancy" [S7, recommendation 2.9; R6].

3. Changed UK clinical practice for the treatment of endometrial hyperplasia

Widespread changes to clinical practice have followed from the guideline change. It is now the case that **over 90% of practitioners use LNG-IUS in their practice**. This is evidenced by a UK-wide survey of gynaecologists, conducted in 2018 through the BSGE and BGCS, in which over 90% reported that they accept the guidelines and follow them in their clinical practice [S8].

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

S1. Assessment of the UK national histopathology database for non-atypical EH.

S2. Testimonial by patient with non-atypical endometrial hyperplasia (July 2020).

S3. Management of Endometrial Hyperplasia. Green-top Guideline No. 67. Royal College of Obstetricians and Gynaecologists/British Society for Gynaecological Endoscopy Joint Guideline. 2016

S4. HKCOG Guidelines. Guidelines on Clinical Management of Endometrial Hyperplasia. Hong Kong College of Obstetricians and Gynaecologists. (September 2015)

S5. British Gynaecological Cancer Society uterine cancer guidelines: Recommendations for practice (2017). Sudha Sundar, Janos Balega, Emma Crosbie, Alasdair Drake, Richard Edmondson, Christina Fotopoulou, Ioannis Gallos, Raji Ganesan, Janesh Gupta, et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 213: 71–97. doi: 10.1016/j.ejogrb.2017.04.015.

S6. The American College of Obstetricians and Gynecologists. Committee opinion number 631 on endometrial intraepitelial neoplasis. May 2015 (reaffirmed 2019). Obstetrics & Gynecology 125(5): 1272-1278. doi: 10.1097/01.AOG.0000465189.50026.20.

S7. ESMO-ESGO-ESTRO consensus conference on endometrial cancer (2016). Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. Ann Oncology 27:16-41. doi:10.1093/annonc/mdv484.

S8. UK wide survey of gynaecologists (2018) to assess acceptance and use of the guideline recommendations for clinical management of endometrial hyperplasia in clinical practice.