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Review article

Efficacy of the LNG-IUS for treatment of endometrial hyperplasia and early stage endometrial cancer: Can biomarkers predict response?

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ABSTRACT

Endometrial Cancer (EC) is the most common gynaecologic malignancy in the developed world, and is increasing in premenopausal women. The surgical standard of care for early-stage EC is not possible in women with concurrent comorbidities or women who desire a fertility sparing approach. The Levonorgestrel Intrauterine System (LNG-IUS) is gaining traction as an alternative treatment for endometrial hyperplasia and early stage EC in inoperable women. Whilst early evidence appears promising, predictive biomarkers need to be established to determine non-responders, which make up one in three women. This timely review discusses the current literature around the identification of clinical, molecular and novel biomarkers that show potential to predict response to progesterone treatment, including the LNG-IUS.

1. Background

Endometrial Cancer (EC) is the most common gynaecologic malignancy in the developed world, making up 3.9% of total cancers in women (Ferlay et al., 2015) and is ranked 14th in terms of mortality (Ferlay et al., 2015). EC incidence is increasing in premenopausal women, with 40% of EC cases attributed to obesity (Li et al., 2019; Kaaks et al., 2002; Scott et al., 2019). This review aims to discuss the need for predictive biomarkers to Levonorgestrel Intrauterine-System (LNG-IUS) treatment for endometrial hyperplasia and early-stage EC. This includes a description of current potential biomarkers, discussion of questions regarding their use, and suggestions for future research in the field.

2. Endometrial hyperplasia and cancer

EC is mainly a hormone-driven cancer with 80% of cancers induced by either oestrogen domination or attenuation of progesterone resulting in a hyperplastic state of the endometrium (Carlson et al., 2012). Early age at menarche, later age of menopause and anovulation can all attenuate physiological progesterone circulation, contributing to the risk of EC (Carlson et al., 2012; Cauley et al., 1989; Van den Bosch et al., 2012). Traditionally, EC was broadly classified into two subtypes known as Bokham type I and type II based on histology (Bokhman, 1983). However, EC classification is now moving towards the use of the TCGA or the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) (Talhouk et al., 2017) system that categorise tumours into *POLE* mutated, Mismatch Repair deficient (MMRd), p53 wild type or p53 abnormal.

Endometrial Hyperplasia is the abnormal, non-invasive proliferation of the endometrial tissue resulting from excess oestrogenic stimulation. All forms of hyperplasia share mutual morphological changes such as an increase in the gland-stroma ratio, and irregularity in both gland shape and size (Silverberg, 2000). The World Health Organisation (WHO94) traditionally classified hyperplasia firstly into hyperplasia with atypia, and hyperplasia without. Secondly, the degree of glandular crowding is assessed giving rise to subgroups of complex and simple hyperplasia (Silverberg, 2000). This classification system has now been updated by the American College of Obstetricians and Gynaecologists and the Society of Gynaecological Oncology, and published by WHO in 2014, which divides hyperplasia into only 2 categories; non-atypical (benign) and atypical/endometrial intraepithelial neoplasia (EIN). This new scheme is superior to the traditional classification methods, and the use of clear guidelines has significant clinical implications for timely investigations and treatment (Sobczuk and Sobczuk, 2017).

Progression of EIN into EC has been reported at rates from 10% (Baak et al., 1992) to 23% (Kurman et al., 1985) and up to 52% (Horn et al.,

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2004) in the absence of treatment. While the sustained exposure to unopposed exogenous or endogenous oestrogen alongside amplified oestrogen/progesterone receptor expression is attributed to hyperplasia progression, there is a myriad of irregularities implicated in the carcinogenic progression of hyperplasia (Ryan et al., 2005).

3. Management of endometrial hyperplasia and early stage cancer

Low dose progestin is the gold standard treatment for simple and complex hyperplasia without atypia (Chandra, xxxx). For atypical hyperplasia, pre-menopausal women are treated via high dose progestin therapy. Currently, the only treatment option for post-menopausal women with atypical hyperplasia, and for any women who do not respond to progestin treatment, is a total hysterectomy (Chandra, xxxx). Therefore, halting the progression of hyperplasia will potentially prevent pre-menopausal women form undergoing a hysterectomy and allow these women to preserve their fertility.

Systemic progestogen therapy, such as medroxyprogesterone acetate (MPA), is efficacious in the treatment of hormone-sensitive hyperplasia and tumours (Mountzios et al., 2011), however, progesterone receptors are often downregulated giving rise to a relatively short therapeutic duration (Gadducci et al., 2006). In addition, systemic therapy is associated with low compliance rates due to adverse systemic effects including nausea, weight gain, abnormal vaginal bleeding and increased risk of breast cancer (Shah et al., 2005).

The standard of care for early-stage EC in medically operable women consists of a hysterectomy with the addition of the surgical removal of a Bilateral Salpingo-Oophorectomy (BSO) and pelvic lymphadenectomy which forms the basis of surgical staging. A BSO is not ideal for younger women as it results in surgical menopause, putting women at risk of long term oestrogen deprivation, which can result in significant cognitive, urogenital and skeletal effects (Angelopoulos et al., 2004). In cases where surgery is not curative, adjuvant therapy is used to treat disease often in the form of brachytherapy (Koh et al., 2018).

4. Comorbidities preventing surgery

Higher BMI complicates the surgical approach due to associated comorbidities such as cardiovascular disease, obesity-hypoventilation syndrome and diabetes-related organ damage. This leads to 10% of women with obesity being deemed inoperable (Acharya et al., 2016), despite this population being more likely to be diagnosed with suspected malignancy (McMahon et al., 2014). Alongside comorbidities, women with obesity are physically more difficult to operate on leading to increased entry attempts for hysterectomy, increased difficulty in identification of landmarks and a reduction in successful completions of the surgery (McIlwaine et al., 2010). Furthermore, postoperative complications are more commonly observed in women with obesity. These include bowel and urologic complications, blood vessel injuries, pelvic hematoma, pelvic infection, pneumonia, increased blood loss, wound complications, and venous thromboembolisms (McMahon et al., 2014; Uccella et al., 2016).

5. LNG-IUS as a therapeutic option for early stage EC and hyperplasia

The LNG-IUS also known as Mirena®, is a common Long Acting Reversible Contraception (LARC) option for women which is also used to treat women with abnormal and heavy bleeding (menorrhagia). Levonorgestrel suppresses endometrial proliferation, producing endometrial atrophy due to decidualization and suppression of the endometrial glands (Beatty and Blumenthal, 2009). The LNG-IUS is gaining traction as an alternative treatment for hyperplasia and early stage EC for those women who are inoperable. The evidence base for the use of LNG-IUS in this setting appears promising; key studies investigating the efficacy of the LNG-IUS for the treatment of hyperplasia and EC are outlined in Table1.

Extensive studies and *meta*-analysis investigating the efficacy of systemic progestin therapy vs LNG-IUS therapy for hyperplasia treatment have shown that LNG-IUS treatment had higher pooled regression rates and lower hysterectomy rates than oral progestogen treatment (Gallos et al., 2010; Gallos et al., 2013; Orbo et al., 2014; Abu Hashim et al., 2015).

Further clinical trials are currently in motion to assess the efficacy of LNG-IUS as a treatment for early stage EC and endometrial hyperplasia. These trials can be seen in Table 2.

The use of the LNG-IUS to treat endometrial hyperplasia and EC appears promising and has been listed as an appropriate therapy by some (National Comprehensive Cancer Network) (Rodolakis et al., 2015), the use of LNG-IUS to treat hyperplasia and early stage EC has yet to be equivocally determined. Importantly, evidence appears that it there is recalcitrance in response to hyperplasia and early stage EC for some women – the reasons for which are not well understood. Farthing *et al.,* noted that due to the ease of LNG-IUS treatment, the information the patient receives from their clinician may not be as specific or accurate as traditional treatment forms, which will require more specialist consultations (Farthing, 2020). Surgery has been proven to be associated with a high cure rate and low morbidity rate when treating EC, particularly in early stages (Chan et al., 2001). Because of this, predictive biomarkers would better tailor LNG-IUS treatment to ensure that women are not exposed to further risk through the use of conservative LNG-IUS treatment instead of surgery. If that risk could be eliminated, then the

Table 1
Studies investigating the efficacy of LNG-IUS treatment of endometrial hyperplasia and EC.

Author	Type of study	Number of participants	EC/ Hyperplasia	Response Rate
Pal et al., 2018	Retrospective study	n = 15	Hyperplasia	80%
Baker et al., 2017	Retrospective study	n = 46	Hyperplasia	80%
Marnach et al., 2016	Retrospective study	n = 94	Hyperplasia	87%
Sletten et al., 2018	Prospective study	n = 21	Hyperplasia	100%
Westin et al., 2020	Prospective study	n = 36	Hyperplasia	90.6%
Leone Roberti Maggiore et al., 2019	Prospective long term follow up study	n = 28	Hyperplasia	89.3%
Varma et al., 2008	Prospective long term follow up study	n = 105	Hyperplasia	90%
Wildemeersch et al., 2007	Prospective long term follow up study	n = 20	Hyperplasia	95%
Scarselli et al., 2011	Prospective long term follow up study	n = 34	Hyperplasia	85%
Orbo et al., 2014	Randomised trial	n = 170	Hyperplasia	100%
Abu Hashim et al., 2015	Randomised trial	n = 59	Hyperplasia	67.8%
Gallos et al., 2013	Comparative cohort study	n = 250	Hyperplasia	94.8%
Westin et al., 2020	Prospective study	n = 21	Grade I EC	66.7%
Leone Roberti Maggiore et al., 2019	Prospective long term follow up study	Grade 1 EC: n = 16 Grade 2 EC: n = 4	Grade 1 EC Grade 2 EC	Grade 1 EC: 81.3% Grade 2 EC: 75%
Pal et al., 2018	Retrospective study	Grade 1 EC: n = 9 Grade 2 EC: n = 8	Grade 1 EC Grade 2 EC	Grade 1 EC: 67% Grade 2 EC: 75%

Table 2
Current clinical trials assessing LNG-IUS efficacy when treating hyperplasia and EC.

Clinical trial number	Additional treatments	Primary Outcome	Biomarkers to analyse	Number of women	Predicted completion date
NCT02035787	Metformin	Response: (LNG-IUS + Metformin)	Ki67	30	December 2022
NCT02990728	Metformin	Response: (LNG-IUS) vs (LNG-IUS + Metformin)	PRB, PRA, ER, Ki67, PTEN, Bcl2	120	March 2020
NCT01686126	Metformin	Response: (LNG-IUS) vs (LNG-IUS + weight loss) vs (LNG-IUS + Metformin)	Non disclosed molecular biomarkers	165	December 2020
NCT02397083	Everolimus	Response: (LNG-IUS) vs (LNG-IUS + Everolimus)	None	270	September 2026
NCT03241914	Megestrol acetate	Response: (LNG-IUS) vs (LNG-IUS + Megestrol acetate)	None	64	June 2020
NCT00788671	none	Response: LNG-IUS	Non disclosed molecular biomarkers	70	November 2020

PRA = Progesterone Receptor A, PRB: Progesterone receptor B.

LNG-IUS may not only be an option for inoperable women, but for all women who wish to preserve their uterus.

There has been some attempts to identify and use clinicopathological markers, however, most studies produce insignificant or conflicting results. This means that current clinicopathological markers are not suitable for guiding LNG-IUS treatment of hyperplasia and EC, and that molecular biomarkers may hold more promise. In their retrospective study, Pal *et al.,* (Pal et al., 2018) identified that increased uterine size (by 1.3 cm) was associated with non-response, however this was not confirmed in a subsequent prospective trial of the LNG-IUS by Westin et al. (Westin et al., 2020; Westin et al., 2020). FIGO 1 EC vs hyperplasia and older age have both been identified as predictors of poor response to progestin therapy (Zakhour et al., 2017). BMI may not be a useful maker of response; five studies have produced contradicting results. Westin et al., (Westin et al., 2020) Pal et al., (Pal et al., 2018) and Ciccone *et al.,* (Ciccone et al., 2019) all found no significant association between BMI and LNG/progestin response. However, Graul *et al.,* (Graul et al., 2018) showed progression was associated with higher BMI, whereas Mandelbaum *et al.,* (Mandelbaum et al., 2020) showed that response was 4 times greater in class III obese women vs non-obese/class II. A BMI > 30 has also been associated with a higher risk of disease regression following conservative treatment than non-obese women (Yang et al., 2015). These studies are based on varying sample sizes from as low as 46 to as high as 245, and included both atypical hyperplasia and endometrial cancer. No further clinical characteristics such as age, parity, metformin use or previous hormone use has been associated with LNG-IUS response (Pal et al., 2018; Westin et al., 2020).

6. Molecular biomarkers for guiding LNG-IUS treatment of hyperplasia and EC

Molecular biomarkers are non-imaging biomarkers that are measurable in biological samples such as plasma, serum or tissue. This includes but is not limited to gene and protein expression, genetic mutations and polymorphisms. The remainder of this review will focus on the current molecular biomarker research around guiding progesterone treatment of hyperplasia and EC as a commentary on the current state of knowledge and what still needs to be done. Few papers investigate biomarkers involved in Levonorgestrel resistance explicitly, with only 3 molecular based studies looking at the effects of the LNG-IUS on cell lines. The majority of studies conducted look into predictive biomarkers for oral progestin treatment and while these may not correlate to LNG-IUS treatment specifically, they are still important to investigate as the LNG-IUS has a similar mechanism of action to oral progestins, but at a more localised level.

6.1. Established markers

Commonly used pathology markers have also been investigated, however the majority of the studies demonstrate no association with protein or gene expression levels of Pax-2/*PAX2*, Bcl-2/*BCL2* (Upson et al., 2012; Gallos et al., 2013; Vereide et al., 2005; Sletten et al., 2017); *BAX* (Vereide et al., 2005; Sletten et al., 2017); *COX-1* or Mlh1 (Gallos et al., 2013).

PR, or its associated isoforms (PRA and PRB) alongside ER or its associated isoforms (ERα and ERβ) are the most investigated IHC markers in progestin treatment of hyperplasia and EC (Travaglino et al., 2019). In their prospective trial, Westin *et al.,* (Westin et al., 2020) showed in a small cohort that responders (31 of 32) had statistically significant evidence of progesterone effect at 3 months compared to non-responders (2 of 8). However, baseline (pre-treatment) expression of progesterone receptor did not have any predictive value. In other studies, low expression of progesterone receptor protein has been associated with a poorer response to progesterone treatment (Upson et al., 2012; Gallos et al., 2013; Akesson et al., 2010; Fawzy et al., 2016; Janzen et al., 2013; Vereide et al., 2006), mostly in regard to systemic progestogen treatment. However, Reyes *et al.,* observed the same in patients treated with LNG-IUS (Reyes et al., 2016) and also showed a relationship between progesterone receptor expression and *FOXO1* mRNA expression, identifying *FOXO1* to be a potential predictive marker to LNG-IUS treatment (Reyes et al., 2016). While this study gains credibility from using biopsy specimens gained from treated women, and performing both IHC and qPCR, it is important to note that the results observed are from 10 women only, making it relatively non-generalisable. The ER has also been investigated as a potential biomarker, with current research showing knockdown or low protein expression of ERα and low mRNA expression of the *ESR1* gene predicts a negative response to progesterone treatment (Akesson et al., 2010; Wik et al., 2013), with Akesson *et al.,* observing the differing ER protein levels specifically in LNG-IUS treatment cohorts (Akesson et al., 2010). Other studies have shown no relationship between ER protein levels and response to progestin treatment (Utsunomiya et al., 2003; Gunderson et al., 2014; Reyes et al., 2016) or ERβ expression and progestin response (Vereide et al., 2006).

Tumour suppressor p53 has been studied as a potential biomarker; one prospective study carried out on 50 hyperplastic patient samples showed that decreased p53 protein expression may be a predictive biomarker of progestin resistance (Fawzy et al., 2016). Patients that failed to respond to progesterone therapy had significantly lower p53 levels than those that showed regression of hyperplasia. However, this is only noted in women with atypical hyperplasia and baseline recordings would be needed to support the claim that p53 acting as a potential predictive marker.

An extensive systematic review has been carried out on IHC markers of response to conservative treatment of endometrial hyperplasia and early stage EC (Travaglino et al., 2019). This paper investigated 31 pre-treatment assessment IHC markers across 19 studies and found that abnormal mismatch repair pattern (abnormal staining of MLH1, MSH2, MSH6 and PMS2), commonly associated with Lynch syndrome, to predict a poor response to progestin treatment of endometrial hyperplasia and early stage EC. This has also been supported by Chung *et al.,* who observed poorer response to progestin/LNG-IUS therapy in MMRd

patients (n = 9) compared to p53wt patients (Chung et al., 2020). It is important to note that there were only 9 women in the MMRd group of this study, therefore further investigations should be carried out in a larger cohort. Travaglino *et al.,* also identified Dusp6, 17β-HSD1 to predict a good response to progestin treatment of both hyperplasia and EC, and GPR78 to predict a negative response to progestin treatment of hyperplasia.

6.2. Novel biomarkers

Discovery based approaches have also been used to identify promising predictive biomarkers for progestin resistance. Li et al., have identified novel markers involved in progestin resistance in one cell line using microarray and microarray, gene ontology and pathway enrichment. *ANO1, SOX17, CGNL1, DACH1, RUNDC3B, SH3YL1* and *CRISPLD1* (Li et al., 2019), were identified to each have the potential to serve as individual predictive biomarkers. This study simply observes this occurrence in one commercial cell line (Ishikawa cells), and is based off MPA resistant cells, rather than the LNG-IUS specifically. More studies utilising additional commercial cell lines as well as pre-treatment tissue from a well-defined cohort with outcome data should be conducted to investigate the significance of these genes and their potential role as predictive biomarkers. More recently, Yang *et al.,* has identified MSX1 as both a specific indicator and therapeutic target for progesterone resistance (Yang et al., 2020).

MSX1 has also been identified as a key differently expressed gene between resistant and non-resistant EC cells using microarray, pathway and gene enrichment analysis. Yang *et al.,* verified this in MPA resistant Ishikawa cells where mRNA levels of MSX1 were significantly higher in resistant cells compared to MPA sensitive controls. Alongside this, MSX1 knockout in these cells led to down regulation of key genes driving proliferation and epithelial to mesenchymal transition, alongside increased sensitivity of cells to MPA (Yang et al., 2020).

6.2.1. PI3K/mTOR/AKT pathway

The AKT pathway has been implicated in progression of numerous cancers and involves key cell regulators such as PTEN, ARIDA1 and KRAS (Pavlidou and Vlahos, 2014). The relationship between Akt-PR has been demonstrated in one endometrial cancer cell line (Ishikawa), with hyperactive signalling upregulating PR transcriptional function (Lee et al., 2016). Furthermore Akt signalling is hyperactive in a progesterone-resistant clone of the same cell line (Ishikawa) and progestin resistance can somewhat be reversed in mouse xenograft models using Akt-inhibitors (Gu et al., 2011; Liu et al., 2017). This indicates Akt, or members of the Akt pathway, could act as predictors of response. However, the prospect of *PTEN* serving as a predictive biomarker in endometrial cancer is inconsistent, with Travaglino *et al.,* showing *PTEN* has no predictive value in the context of both systemic and local progestin treatment including LNG-IUS, MPA, Norethindrone acetate and Melengestrol Acetate in a systematic review of seven studies in women with hyperplasia and EC (Travaglino et al., 2018). However Janzen *et al.*, observed in a mouse model of EC, that low expression of *PTEN* alongside PR and *KRAS* activation could predict a negative response to progesterone treatment (Janzen et al., 2013).

6.2.2. WNT pathway

The Wnt pathway governs normal endometrial homeostasis and aberrant signalling has been implicated in endometrial cancer progression (Coopes et al., 2018), therefore it is likely that it may play a role in LNG resistance. Westin *et al.,* (Westin et al., 2020) measured mRNA expression on key Wnt genes at baseline and at 3 months biopsy including *SFRP1/4*; *DKK3*, *FZD8/10*, *TCF7* and *WNT5A*. Only baseline expression of DKK3 was significantly different between responders and non-responders, with lower expression associated with non-responders. Significantly higher expression of FZD8 and SFRP1in non-responders was observed in the 3 month biopsies. DKK3 should be further evaluated as a biomarker via IHC on these samples, or in an additional prospective trial.

6.2.3. ARID1A

ARID1A knockout has been seen to promote primary resistance to progesterone (Medroxyprogesterone acetate) treatment via down-regulation of progesterone receptor B in EC cells (Ishikawa), meaning it could serve as a potential predictive marker to LNG-IUS treatment (Wang et al., 2019). At this stage, baseline and post-treatment mRNA levels of *ARID1A* have only been investigated in one cell line, leaving validation room for new studies to be carried out on human samples and primary cell lines.

6.2.4. HOTAIR

The *HOTAIR* gene has been implicated in the enhancement of sensitivity to progestin (MPA) in EC cells (Ishikawa, HEC-1A, HEC-1B and AN3CA) through epigenetic regulation of progesterone receptor isoform B (PRB) (Chi et al., 2019). *HOTAIR* was found to be inversely related to PRB expression in human EC tissues. Further investigations showed that knockdown of *HOTAIR* promotes PRB expression, which promotes sensitivity of progesterone treatment both in vitro (Ishikawa, HEC-1A) and in vivo through subcutaneous graft tumour models in nude mice. (Chi et al., 2019). So far, HOTAIR has only been implicated in the progesterone resistance mechanism, therefore, future studies should look at the differences in *HOTAIR* expression between progesterone resistant and non-resistant cells or patients in order to be able to identify this as a predictive biomarker.

6.2.5. HE4

Baseline serum *HE4* has been investigated as a potential biomarker to monitor the efficacy of the LNG-IUS in atypical hyperplasia and early-stage EC (Behrouzi et al., 2020). It is suggested that higher levels of serum *HE4* during and following treatment indicate a negative response to treatment in early stage EC and atypical hyperplasia as a significant reduction is seen from baseline after three months of LNG-IUS treatment and no significant changes are seen in responders. Due to this study relying on baseline *HE4* serum readings, supplementary studies conducted on these readings should use larger populations as it would aid in determining accurate *HE4* serum cut-offs for response vs non-response to confirm the findings from this study. It is also noted that a positive association exists between age and baseline serum *HE4*, so age-adjusted cut-offs will also need to be determined for this information to be deemed clinically relevant (Behrouzi et al., 2020). Orbo *et al.*, also conducted a multicentre randomized control trial studying *HE4* in relation to progesterone treatment, both MPA and LNG-IUS, and found that an increase in the expression of *HE4* during and following progestin therapy regimens can predict a negative therapy response, indicating progestin resistance for medium and low risk endometrial hyperplasia (Ørbo et al., 2016). Interestingly, Orbo *et al.,* found this in EC tissue samples, unlike Behrouzi *et al.,* who found that *HE4* was only relevant in serum samples (Behrouzi et al., 2020). *HE4* could be used clinically as a biomarker to monitor the efficacy of the LNG-IUS throughout the treatment course of EC but at this stage, only shows use as a predictive biomarker for progestin treatment of hyperplasia.

7. Conclusion

Recent therapeutic advances in the oncology field have been driven by the recognition of genetic variations between individual's tumours and using this to identify biomarkers that can predict response to novel and targeted therapeutics. Additional research into pathogeic genes previously studied alongside identification of new ones is clearly warrented and as currently, there are no predictive biomarkers used clinically in relation to LNG-IUS treatment. Predictive molecular biomarkers for the use of LNG-IUS will improve women's outcomes and help reduce long-term morbidity associated with the current treatment paradigm,

and would advance the application of precision medicine in gynaecologic oncology.

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Disclosure of Interest

There are no conflicts of interest to declare.

Contribution of authorship

MD completed the collation and analysis of literature, and drafted the manuscript. SF and KD contributed to manuscript edits and feedback. CH is PI and advised on manuscript conception, analysis and editing. All authors accept responsibility for publication.

Ethics

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Declaration of Competing Interest

The authors declare no potential conflicts of interest.

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