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Guidelines on Clinical Management of Endometrial Hyperplasia

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1 INTRODUCTION

Endometrial hyperplasia represents a spectrum of pre-malignant conditions of the endometrium with varying degrees of malignant potential. It is a recognized precursor lesion for type I endometrial adenocarcinomas (i.e. endometrioid adenocarcinomas). The primary aetiology is believed to be continuous stimulation of the endometrium by oestrogen unopposed by adequate levels of progestogen.

The incidence of endometrial hyperplasia peaks in the sixth decade of life, but it can occur among women of reproductive age (Reed et al, 2009a). Common risk factors include: (i) chronic normo-gonadotrophic anovulation (e.g. polycystic ovary syndrome) leading to long term exposure to unopposed endogenous oestrogen, (ii) exposure to exogenous unopposed oestrogen, and (iii) obesity.

Affected women usually present with abnormal vaginal bleeding. Ultrasound examination of the uterus may reveal a thickened endometrium, although endometrial thickness may show large variations in reproductive age women. Hysteroscopically, the endometrial lining may appear thickened or polypoid although it may vary, and the definitive diagnosis should be made histologically.

2 PATHOLOGY OF ENDOMETRIAL HYPERPLASIA

In the new WHO classification revised in 2014, endometrial hyperplasia is classified into two groups only, namely "non-atypical" and "atypical" hyperplasia.

In cases of "endometrial hyperplasia with focal atypia" on endometrial biopsy or curettage, clinicians should request peer review of histology, and obtain additional samples for evaluation before any surgery is considered (Grade D recommendation).

There have been many classification systems proposed in the literature. The World Health Organization (WHO) system has been the most widely used. Other systems such as the endometrial intraepithelial neoplasia (EIN) system and the European system are also sometimes used.

In the WHO 2004 system for assessing endometrial hyperplasia, the density of the glands, the architecture of the glands, and cytology of the lining epithelial cells are considered. The gland-to-stroma ratio in hyperplasia almost always exceeds 3:1, although mimickers should be taken into consideration. Architecturally, the glands may show cystic dilatation, budding, branching, papillary projections, gland fusion or formation of large glands with multiple lumens (cribriform glands), or combinations thereof. Cytologic atypia is subject to substantial interobserver variation. It is usually characterized by a combination of loss of nuclear polarity, variation in nuclear size and shape, clumping and vesicular chromatin, and prominent nucleoli. The last feature has been said to be the most reproducible in some studies. Assessment of cytologic atypia is best performed when the appearance of the glands in question are compared with the background proliferative endometrium, if present.

Recently, the WHO classification is revised in 2014 (Zaino et al, 2014), under which the architectural pattern is no longer considered. Endometrial hyperplasia is divided into:

- Endometrial hyperplasia without cytological atypia (non-atypical hyperplasia)
- Endometrial hyperplasia with cytological atypia (atypical hyperplasia)

In limited samples such as those from endometrial aspiration or curettage, cytologic atypia may be a focal finding such that a dimorphic pattern of normal and abnormal endometrium is seen. For pathologists, the degree and extent of such abnormality should be emphasized in biopsy reports. Under such circumstances, clinicians should request peer review of histology, and should carry out curettage or obtain additional samples before any radical surgery is considered. It has been reported that patients diagnosed with "endometrial hyperplasia with *focal* atypia" have been treated successfully with conservative methods.

The malignant potential is mainly predicted by cytological atypia. The likelihood of concurrent endometrial cancer varies according to the type of endometrial hyperplasia. About 40-50% of women diagnosed with atypical endometrial hyperplasia have underlying endometrial cancer concurrently. In those with simple or complex hyperplasia without atypia, the prevalence of underlying endometrial cancer is not definitely known; in most centres not all of these cases are treated surgically and hence a definitive histological diagnosis is not always available.

About 30% of women with complex atypical endometrial hyperplasia would have subsequent progression to endometrial cancer, whereas the risk is below 5% with endometrial hyperplasia without atypia. (Kurman et al, 1985; Lacey and Chia, 2009).

3 DIAGNOSIS OF ENDOMETRIAL HYPERPLASIA

If endometrial hyperplasia is diagnosed on endometrial biopsy, it would be reasonable to follow up with diagnostic hysteroscopy with targeted biopsy or dilatation and curettage to rule out carcinoma or atypical endometrial hyperplasia before commencement of treatment (Grade D recommendation).

If hysteroscopy is performed, targeted biopsy should be performed as the diagnostic accuracy of hysteroscopy alone was found to be only modest for cancer or hyperplasia (Grade A recommendation).

If endometrial hyperplasia is diagnosed on endometrial biopsy, it would be reasonable to follow up with diagnostic hysteroscopy and targeted biopsy or dilatation and curettage to rule out carcinoma or atypical endometrial hyperplasia before commencement of treatment. The rate of co-existing carcinoma in patients found to have endometrial hyperplasia without atypia on endometrial biopsy is poorly documented (Lacey Jr & Chia, 2009). On the other hand, the limitation of endometrial biopsy is well known (Daud et al, 2011). Although there is no good evidence to support the need for additional investigation, this would be reasonable in view of the limitation of endometrial biopsy. In a review by Dijkhuizen et al (2000), the detection rate of endometrial biopsy for endometrial carcinoma was 91% for premenopausal women. There are authors who suggest that hysteroscopy with targeted biopsy is better than dilatation and curettage but there is no conclusive evidence to support this claim in this particular group of patients. If hysteroscopy was performed, targeted biopsy should be performed as the diagnostic accuracy of hysteroscopy alone was found to be only modest for cancer or hyperplasia (Clark et al 2002).

4 ENDOMETRIAL HYPERPLASIA WITHOUT ATYPIA

4.1 Conservative vs surgical therapy

Hysterectomy should not be the first line treatment for patients diagnosed to have endometrial hyperplasia without atypia unless there is other indication

for hysterectomy. Conservative management is recommended for endometrial hyperplasia without cytological atypia (Grade B recommendation).

In a review, it was concluded that the risk of subsequent progression to malignancy in women with non-atypical hyperplasia was less than 5% (Lacey & Chia 2009). Hysterectomy should not be the treatment of choice for patients diagnosed to have endometrial hyperplasia without atypia unless there is other indication for hysterectomy. One exception may be in a postmenopausal woman where a source of unopposed oestrogen cannot be identified.

4.2 Conservative medical therapy

Levonorgestrel intrauterine system (LNG-IUS) should be the first line treatment for endometrial hyperplasia without atypia, especially in patients who need contraception (Grade A recommendation).

Oral progestogen is an acceptable alternative. Different regimens of oral progestogens have been used to treat endometrial hyperplasia but there is no consensus on the best regimen (Grade C recommendation). If oral progestogen is used, a continuous regimen may be considered (Grade A recommendation).

Other treatments like observation, combined pills, GnRH agonist, endometrial ablation should not be offered on a routine basis (Good Practice Point).

Progestogens have been used for the treatment of endometrial hyperplasia without atypia. There were many reports on the use of levonorgestrel intrauterine system (LNG-IUS), and long term treatment results are also available (Scarselli et al, 2011). Several randomized control trials have shown that LNG-IUS is more effective than cyclical oral progestogens (Hashim et al, 2013; Ismail et al, 2013; Orbo et al, 2014). Other hormonal contraceptive methods have not been reported as treatment for endometrial hyperplasia (Whiteman et al, 2010).

Various types of oral progestogens including norethisterone (usually at 10-15 mg/day), medroxyprogesterone acetate (usually at 10-20 mg/day), and megestrel (160-320 mg/day) have also been reported to be useful. The progestogens were given continuously or cyclically (for 10-14 days in the second half of the cycle). The duration of treatment varied from 3-6 months. However, most of the reports are retrospective and the numbers of subjects involved were small.

The type of progestogens does not appear to be important, and the optimal dosage of progestogens has not been investigated and the regimens advocated are essentially empirical (Marsden & Hacker, 2001; Ozdegirmenci et al, 2011). A summary of the data available is listed in Table 1. It is clear that prospective studies had small number of patients and different regimens of different types of progestogens have been tested. In the only ‘prospective observational’ study with more than 100 patients, data were extracted from structured medical records and at least eight types of treatment were given (Rattanachaiyanont et al, 2005). One randomised study comparing three different regimens of progestogens was identified but no difference in efficacy was found (Ozdegirmenci et al, 2011). One study found that cyclical progestogens was less effective compared with continuous oral therapy and LNG-IUS (Orbo et al, 2014). In the other two randomized studies mentioned (Hashim et al, 2013; Ismail et al, 2013), cyclical progestogens was less effective compared with LNG-IUS. If oral progestogen is used, a continuous regimen may be considered.

Other treatment options including observation, combined pills, GnRH agonist, endometrial ablation have been suggested but data supporting their routine use is limited.

Table 1. Literature review of oral and injectable progestogen treatments for endometrial hyperplasia without cytological atypia

Authors	Type of study	N	Regimen	Duration		Regression rate
Gal et al 1983	prospective	29	megestrol acetate 40 mg qd	13-96 months	continuous	89.6%
Ferenczy & Gelfand 1989	prospective	65	MPA 10 mg qd for 14 days per month, reduce to 5 mg qd for 11 days per month when histology return to normal	?	cyclical	80%
Guven et al 2001	prospective	24	megestrol 160-320 mg qd	3 months	continuous	79.1%
Horn et al 2004	retrospective	208	NET 5 mg qd for premenopausal patients, MPA 10 mg qd for perimenoapusal patients; MPA 20-50 mg qd for postmenopausal patients	3-5 months	continuous	61.5%
Jarvela & Santala 2005	RCT	17	MPA 10 mg qd for 10 days for premenopausal patients, MPA 10 mg qd for postmenopausal patients	3 months	cyclical or continuous	65%
Rattanachaiyanont et al 2005	prospective	104 19 10 1	1. MPA 10 mg qd for 12-14 days per cycle 2. NET 10 mg qd for 12-14 days per cycle 3. Other cyclic progestins: medrogestone 10 mg qd, dydrogesterone 20 mg qd for 12-14 days per cycle 4. Other continuous progestins: MPA 2.5 mg qd or 150 mg depo-MPA monthly	6 months	cyclical or continuous	92.3% 89.4% 100% 100%
Bese et al 2006	prospective	19	NET 15 mg qd for 10 days for 3 months	3 months	cyclical	100%
Vereide et al 2006	prospective	21	MPA 10 mg qd for 10 days per cycle	3 months	cyclical	51.7%
Milam et al 2008	retrospective	13	MPA or megestrol or NET ?dose	1-12 months	?	42.1%
Buttini et al 2009	retrospective	10	MPA 10-20 mg qd	?	?	90%
Reed et al 2009	retrospective	185	MPA or megestrol or NET at different doses	14 days to 6 months	?	71.6%
Ozdegirmenci et al 2011	RCT	30 25 27	1. MPA 10 mg qd for 10 days per cycle 2. lynestrenol 15 mg qd for 10 days per cycle 3. NET 15 mg qd for 10 days per cycle	3 months	cyclical	96.6% 100% 96.3%
Dolapcioglu et al 2013	RCT	26 26	1. MPA 10 mg qd for 10 days per cycle 2. MPA 10 mg qd for 10 days per cycle	3 months 6 months	cyclical	88.5% 96.1%
Hashim et al 2013	RCT	61	NET 15 mg qd for 3 weeks per cycle	3-6 months	cyclical	60.7%
Ismail et al 2013	RCT	30 30	1. MPA 10 mg qd for 10 days per cycle 2. NET 15 mg qd for 10 days per cycle	3+3 months	cyclical	96.6% 96.6%
Orbo et al 2014	RCT	47 40	1. MPA 10 mg qd for 10 days per cycle 2. MPA continuous 10 mg qd	6 months	cyclical, continuous	70.2% 97.5%

N=number of patients with non-atypical hyperplasia
MPA= medroxyprogesterone acetate; NET= norethisterone; RCT = randomized control trial
? = unknown

4.3 Monitoring and subsequent management

The first histological monitoring can be performed 6 months after commencement of treatment (Grade C recommendation).

After completion of treatment, it is reasonable to follow up these patients for 2 years with periodic endometrial sampling even if the pathology regresses (Grade C recommendation).

On discharge from further follow up, these patients should be informed of the risk of late recurrence and to consult doctors should abnormal uterine bleeding occur (Good Practice Point).

The first histological monitoring can be performed 6 months after commencement of treatment. A similar protocol was reported for oral progestogen therapy (Rattanachaiyanont et al, 2005). Varma et al (2008) reported that the mean time for regression of simple and complex endometrial hyperplasia were 6.2 (95% CI 4.4-8.0) months and 9.4 (95% CI 7.0-11.7) months respectively.

After completion of treatment, it is reasonable to follow up these patients for 2 years with periodic endometrial sampling if pathology regresses (Scarselli et al 2011). Eighty per cent of persistent/recurrent endometrial hyperplasia were observed early after LNG-IUS removal. On discharge from further follow up, these patients should be informed of the risk of late recurrence and to consult doctors should abnormal uterine bleeding occur.

4.4 Further management if pathology persists

If pathology persists at 6 to 12 months after oral progestogen therapy, insertion of LNG-IUS can be considered (Grade C recommendation).

If pathology persists 6 months after insertion of LNG-IUS, assessment can be repeated after another 6 months (Grade C recommendation).

Hysterectomy should be considered if there is no response after insertion of LNG-IUS for a year (Good Practice Point).

If pathology persisted at 6 to 12 months after oral progestogen therapy, insertion of LNG-IUS can be considered because of the higher efficacy reported in the treatment of complex hyperplasia. (Gallos et al 2010) If pathology persisted 6 months after insertion of LNG-IUS, assessment can be repeated after another 6 months. This is because regression of complex endometrial hyperplasia may take up to 11.7 months. Hysterectomy should be considered if there is no response after insertion of LNG-IUS for a year.

5 MANAGEMENT OF ENDOMETRIAL HYPERPLASIA WITH CYTOLOGICAL ATYPIA

5.1 Conservative (medical) vs surgical treatment

Total hysterectomy is the standard treatment. In women with a desire to preserve fertility, however, medical treatment may be considered after proper counseling (Grade D recommendation).

In view of the risks of concurrent or progression to endometrial cancer, the treatment of choice should be surgical i.e. total hysterectomy. However, there are increasing evidences that medical therapy can be safe and effective as a primary treatment in young, nulliparous women who refuse surgical approach in order to preserve their reproductive potential. Therefore, women with atypical disease can be managed medically if fertility consideration or other medical factors precluding surgery are present and that patients have been counseled

regarding disease progression or diagnostic under-call.

5.2 *Modalities and efficacy of medical treatment*

For women who opt for conservative management for atypical hyperplasia, oral progestogen or LNG-IUS may be considered. There is no consensus on the best regimen.

Progestin therapy: Because endometrial hyperplasia is estrogen dependent, progestins are used to induce regression. It appears to decrease glandular cellularity by triggering apoptosis. Common used progestins are medroxyprogesterone acetate (orally or IMI injection), megestrol acetate (orally) and levonorgestrol (locally through IUCD). The dosage, duration, types of progestin and routes of administration are different in different studies. In general, the regression rate is 70% to 90%. (Table 2)

Table 2. Literature review of medical treatments for endometrial hyperplasia with cytological atypia

Author	Type of study	N	Regimen	Duration	
Perez-Medina et al, 1999	Prospective	16	NETA 500mg weekly for 3 months + Triptorelin depot 3.75 mg monthly for 6 months	6 months	Continuous
Grimbizis et al, 1999	Prospective	3	Triptorelin 3.75 mg IMI monthly	6 months	Continuous
Clark et al, 2006	Retrospective	73	LNG-IUS, oral progestogens, other hormones, endometrial ablation, total abdominal hysterectomy	Variable	Continuous and cyclical
Wheeler et al, 2007	Retrospective	44	LNG-IUS, oral progestogens	Up to 25 months	Continuous and cyclical
Wildemeersch et al, 2007	Prospective	8	LNG-IUS	14-90 months	Continuous
Orbo et al, 2008	Prospective	370	MPA 5 mg daily, LNG-IUS	6 months	Continuous
Varma et al, 2008	Prospective	9	LNG-IUS	Up to 5 years	Continuous
Signorelli et al, 2009	Prospective	21	Progesterone 200 mg daily oral D14-25	Up to 2 years	Cyclical
Reed et al, 2009b	Retrospective	70	Megestrol, MPA, NETA of various doses and duration by oral route	Variable (> 8 weeks)	Continuous or cyclical
Buttini et al, 2009	Retrospective	21	LNG-IUS, oral MPA 10-20 mg daily	Up to 40 months	Continuous
Gallos et al, 2010	Retrospective (meta-analysis)	1001	LNG-IUS and oral progestogens of variable dose and duration	Variable	Continuous or cyclical

N= number of patients with atypical endometrial hyperplasia
NETA=norethindrone acetate; MPA=medroxyprogesterone acetate; LNG-IUS = levonorgestrel intrauterine system

GnRH analogue therapy: From the few studies reported, GnRH analogue appears to be ineffective for treatment of atypical hyperplasia unless it is used together with progestin. (Agorastos et al, 1997; Pérez-Medina et al, 1999).

5.3 Monitoring and subsequent management plan when conservative management is adopted

For patients with no fertility wish who opt for conservative management, endometrial sampling can be repeated 3 monthly until two consecutive normal results are obtained. Endometrial sampling can subsequently be repeated 6 monthly or when abnormal bleeding occurs, preferably for 5 years (Grade D recommendation).

For patients with fertility wish, endometrial sampling can be repeated 3 monthly until 2 normal consecutive results are obtained. The patient may then be referred to the reproductive medicine specialist for consideration of fertility treatment (Grade D recommendation).

Most of the data on conservative management were on the use of high dose progestogens or LNG-IUS with a duration of at least 6 months. When an oral progestogen is used, endometrial sampling should be performed 3-monthly for twice, and 6-monthly thereafter. When LNG-IUS is used, monitoring should be performed by 3-monthly endometrial sampling for twice and if both are normal, repeated if clinically necessary afterwards.

There is also no consensus for the duration of follow up, however, should fertility be concerned, patient should be referred to specialist once normal endometrial sampling for twice is reached.

5.4 Role of gynaecological oncology expertise in surgical management

There is no evidence that involvement of a gynae-oncologist will improve the survivial in surgical management of complex endometrial hyperplasia with atypia (Grade D recommendation).

Since the risk of co-exisiting advanced stage cancer of the uterine corpus even in cases of complex endometrial hyperplasia with atypia is extremely low, it is unnecessary to involve a gynaecological oncologist in such management.

The prognosis of cancer of the uterine corpus is good and there is no evidence that involvement of a gynae-oncologist will improve the survivial. In addition, the surgical treatment is simple hysterectomy, and lymph node dissection should not be performed without histological proof of invasive disease.

6 REPRODUCTIVE ISSUES IN WOMEN WITH ENDOMETRIAL HYPERPLASIA

6.1 Fertility treatment after treatment of endometrial hyperplasia

It is not possible to conclude if there is any adverse effect of endometrial hyperplasia on the fertility and pregnancy rate of assisted reproduction (Grade D recommendation).

Fertility treatment can be commenced after six months since histological regression (Grade D recommendation).

All articles reviewed (Table 3) were case reports with small numbers of subjects, and many contained cases with either endometrial carcinoma or endometrial hyperplasia. It was not clear in some studies if there was complete regression of endometrial hyperplasia prior to fertility treatment. There were no details about the fertility workup, presence of other infertility factors and assisted reproduction methods. There was also lack of any comparison to a control group without endometrial hyperplasia.

In the recent review by Gadducci et al. (2009), it was commented that the large majority of women attempting to conceive after the completion of hormonal treatment have become pregnant with the aid of assisted reproductive technology. The implementation of IVF techniques not only increased the chance of successful conception, but it might also decrease the interval to conception.

Table 3: Pregnancies after fertility-sparing hormone treatment in patients with endometrial hyperplasia

Studies	Endometrial result prior to pregnancy	No. of patients	No. with fertility wish	No. who conceived	No. who delivered babies	Fertility Treatment
Goker et al., 2001	?	1	1	1	1	IVF
Kaku et al., 2001	Remission	18		5	4	CC CC/HMG
Lowe et al., 2003	Proliferative	2	2	1	1	IVF
Piura et al., 2006	Decidual changes (Small foci of well-differentiated endometrioid carcinoma before Px)	1	1	1	1 (two deliveries)	IVF
Ushijima et al., 2007	Absence of hyperplaisa	17	7	7	4	CC HMG IVF
Qi et al., 2008	Atropic / Secretory	2	2	2	2	Ovulation induction CC and HMG
Signorelli et al., 2009	?	10	10	5	Not stated	IUI
Han et al., 2009	Remission	3	3	2	2	HMG and IUI
Yu et al., 2009	Remission	17	10	4	3	Ovulation induction
Ercan et al., 2010	?	1	1	1	1	IVF
Minig et al., 2011	Remission	20	?	8	6	Ovulation induction

Most published reports were small retrospective series or case reports that often included women with atypical hyperplasia as well as well-differentiated adenocarcinoma of the endometrium. Treatment is usually initiated once complete remission has been confirmed and there is no specified "disease-free" time interval. Assisted reproductive technology is used in the majority of cases to save time.

The following is a summary table of the reported cases; those solely concerned with young women diagnosed with adenocarcinoma of the endometrium were not included. A summary was presented in a review by Gadducci (2009).

Authors	Response rate	Recurrence	No. who conceived	No. who delivered healthy babies
Muechler et al, 1986	1	-	1	1
Randall et al, 1997	EC 75% (9/12); AH 94% (16/17)	-	3/12 (25%), 2/17 (12%)	5
Goker et al, 2001	AH	-	1	1
Kaku et al, 2001	83% (15/18)	-	5/18 (28%)	4
Lowe et al, 2003	100% (2 EC, 2 AH)	-	3/4 (75%)	8 (5 pregnancies)
Jadoul et al, 2003	EC 80% (4/5); AH 100% (2/2)		4/5 (80%), 1/2 (50%)	4
Piura et al, 2006	-	-	1	1
Minaguchi et al, 2007	92% (11/12)	36% (4/11)	5/9 (56%)	?
Ushijima et al, 2007	Overall 67% (30/45); AH: 82% (14/17)	50% (15/30)	12	7
Qi et al, 2008	AH 100% (2/2)	-	2	2
Han et al, 2009	-	-	80% (8/10) → 4 IVF & 6 COH ± IUI	6
Yu et al, 2009	EC 75% (6/8); AH 100% (17/17)	-	4 (AH)	3
Ercan et al, 2010	100% (1/1)	0%	1	2 (twins)
Minig et al, 2011	95% (13/14)	5% (1/14)	9	1

6.2 Effects of fertility drugs or ovarian stimulation on endometrial hyperplasia

The use of fertility drugs in women with endometrial hyperplasia should not be considered as contraindicated. There is no good evidence there is an association between use of fertility drugs and endometrial carcinoma (Grade D recommendation).

There are no relevant studies addressing any adverse effects of fertility drugs or ovarian stimulation on the progress of endometrial hyperplasia.

The relationship between the fertility drugs and endometrial carcinoma has been examined in general patients. Some cohort studies have not observed any association (Venn et al., 1999;

Potashnik et al., 1999; Klip et al. 2002). In an Israeli study, there was a significant two-fold increase in risk of endometrial carcinoma following the use of fertility drugs (clomiphene or HMG) for patients treated between 1964 and 1974 (Modan et al. 1998). A multi-centre US study found that use of clomiphene was associated with a non-significant increase in risk (RR 1.8 95% CI 0.9-3.3) (Althuis et al. 2005). Uterine cancer risk increased with the dose of clomiphene and among nulligravid and obese women. On the other hand, no excess risk for endometrial carcinoma was noted in a cohort of women treated with IVF (Dor et al., 2002).

7 CONTRACEPTIVE USE IN WOMEN WITH CURRENT OR PAST HISTORY OF ENDOMETRIAL HYPERPLASIA

The use of LNG-IUS is safe for women with endometrial hyperplasia (Grade A recommendation).

There is no contraindication for the use of other hormonal and non-hormonal contraceptive methods in women with current or past history of endometrial hyperplasia (Grade D recommendation).

A recent systematic review (Whiteman et al, 2010) studied evidence from 9 cohort and non-comparative studies, 8 of which included women with atypical endometrial hyperplasia. Out of the 9 studies reviewed, 7 showed disease regression in all subjects. One reported disease regression in 90% of subjects, with all the remaining having disease persistence without progression. One showed disease regression in 72% of subjects and it did not distinguish between disease persistence from progression in the remaining. Therefore, the use of LNG-IUS is safe for women with endometrial hyperplasia, and may in fact have therapeutic effects as discussed above.

There has not been study on the safety of use of other contraceptive methods in women diagnosed with endometrial hyperplasia. A systematic review suggested that the use of all the combined or progestogen-only contraceptive methods is protective against rather than predisposing to endometrial cancer (Mueck et al, 2010). Hence, there is no theoretical concern over the use of hormonal or non-hormonal contraceptive methods in such situation, all of which are classified as Category 1 in the US Medical Eligibility Criteria for Contraceptive Use (2010).

8 USE OF HORMONE REPLACEMENT THERAPY (HRT) AND RELATED AGENTS IN WOMEN WITH HISTORY OF ENDOMETRIAL HYPERPLASIA

The use of HRT in women with history of endometrial hyperplasia is probably safe in the absence of other medical contraindications (Grade C recommendation).

There is no study directly addressing on the use of HRT in women with history of endometrial hyperplasia. A Cochrane review confirmed that unopposed oestrogen was associated with increased risk of endometrial hyperplasia at all doses, but the use of combined HRT was not associated with any increased risk of endometrial hyperplasia compared to placebo in women with intact uterus (Furness et al, 2009). Raloxifene, unlike tamoxifen despite both being selective oestrogen receptor modulators, does not seem to increase risk of endometrial hyperplasia (Pinkerton and Goldstein, 2010). It has also been suggested that HRT can be used without strong evidence of deleterious effects in survivors of endometrial cancer (Hinds and Price 2010; MacLennan 2011; King et al, 2011).

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This guideline was produced by the Hong Kong College of Obstetricians and Gynaecologists as an educational aid and reference for obstetricians and gynaecologists practicing in Hong Kong. The guideline does not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognized clinical methods and techniques for consideration by practitioners for incorporation into their practice. It is acknowledged that clinical management may vary and must always be responsive to the need of individual patients, resources, and limitations unique to the institution or type of practice. Particular attention is drawn to areas of clinical uncertainty where further research may be indicated.