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RESEARCH ARTICLE

HOW MANY PREGNANCIES ARE ALLOWED AFTER FERTILITY PRESERVING MANAGEMENT OF ATYPICAL ENDOMETRIAL HYPERPLASIA?

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Abstract

Atypical endometrial hyperplasia,with fertility preserving management by hormonal IUS,and oral progesterone, natural conception three times,allowed for how many pregnancies before hysterectomy? To reduce the incidence of endometrial cancer.

Introduction:-

Endometrial cancer (cancer of the lining of the womb) is the fifth most common cancer in women worldwide (Bray 2013), and the fourth most common cancer in women in high-income countries where its incidence is increasing. (Bray 2013; Cancer Research 2015)**.** Each year approximately 319,605 new cases of endometrial cancer are diagnosed worldwide; 9000 of these in the UK and 61,380 in the USA (Cancer Research 2015; SEER 2015).

Endometrial hyperplasia is an overgrowth of the womb lining and can be a precursor to some types of endometrial cancer. It is a proliferative endometrial lesion. The incidence of endometrial hyperplasia is 133 per 100,000 women per year, and of atypical endometrial hyperplasia is 54 per 100,000 women per year

The 2014 World Health Organization (WHO) classification of endometrial hyperplasia includes only two categories: hyperplasia without atypia, and atypical hyperplasia/endometrial intraepithelial neoplasia (Zaino 2014). This reduction to just two categories includes new findings on molecular genetic changes. Hyperplasia without atypia has no significant genetic changes and usually regresses. Atypical endometrial hyperplasia shares many mutations (microsatellite instability, paired box gene2 (PAX2) inactivation, phosphatase and tensin homolog (PTEN), KRAS, CTNNB1 (β-catenin) mutation) with endometrioid endometrial cancer and has a high co-incidence or conversion to endometrial cancer (Zaino 2014)

Hyperplasia with and without atypia have different rates of progression to cancer. Hyperplasia without atypia has a reported progression rate of 1% to 5% (Kurman 1985; Lacey 2010), whereas atypical hyperplasia progresses in as many as 8% to 27% of cases, and this may be an underestimate, since co-existing carcinoma has been reported in 36% to 59% of women undergoing hysterectomy for atypical endometrial hyperplasia (Antonsen 2012; Kurman 1985; Lacey 2010; Rakha 2012; Zaino 2014).

Endometrial cancer is most common in postmenopausal women. However, between 15% to 25% of cases are diagnosed in premenopausal women (Barakat 2006; Creasman 2001; Lee 2007; Siegel 2015). Four per cent of cases occur in women under the age of 40, and 7% to 10% in women under the age of 45 (Barakat 2006; Creasman 2001; Lee 2007; Navarria 2009; SEER 2015)

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There are several types of endometrial cancer. Endometroid adenocarcinoma of the endometrium is the most common and is often diagnosed at an early stage, which usually has a very good prognosis (ACS 2017). In young women, five- and 10-year disease-free survival (DFS) after standard surgical treatment (hysterectomy and bilateral salpingo-oophorectomy) is 99.2% and 98% (Crissman 1981; Lajer 2012). In addition, it is commonly thought that young women with endometrial cancer are more likely to have early stage, low-risk tumours. However, in a population-based registry, only 18% of women younger than 45 years of age had a stage IA grade 1 endometrial cancer (Navarria 2009)

The main risk factor for endometrial hyperplasia and endometrioid endometrial adenocarcinoma is obesity. Obesity is associated with the peripheral conversion of androgens to oestrogens by adipose tissue (Chen 2017). Other risk factors include a sedentary lifestyle, hyperinsulinaemia, diabetes, hypercholesterolaemia, hypertension, nulliparity, early menarche and anovulation (Corzo 2018), but many of these factors are related to, and not independent of, obesity. Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder associated with anovulation (Gottschau 2015), and it is also a common cause of infertility. Therefore, in women with PCOS, there may be an increase in peripheral conversion of oestrogens and also the associated anovulation results in lack of progesterone release. Progesterone is produced in ovulatory cycles by the ovarian corpus luteum. Furthermore, nulliparity itself is a risk factor for endometrial cancer and is inversely related to parity, since nulliparous women miss out on periods of high progesterone levels during a pregnancy (Wu 2015; Yang 2015)

Young nulliparous women with endometrial carcinoma may be interested in fertility-sparing treatment. These women should be informed that standard surgical treatment for endometrial cancer/atypical hyperplasia has excellent survival results, but prevents fertility. Unfortunately, many of these women will have underlying subfertility, so, even without a diagnosis of atypical hyperplasia or endometrial cancer, the chance of becoming pregnant may be low. Fertility after conservative treatment for endometrial atypical hyperplasia and cancer will depend on the response to cancer treatment and also on underlying patient factors affecting fertility (e.g. presence of PCOS) . Discussion about appropriateness of fertility-sparing surgery should therefore balance potential risks with a realistic discussion about the chance of achieving a pregnancy on an individual basis. Ovulation induction treatment may be necessary (Jin 2018), which may be associated with an increased risk of endometrial atypical hyperplasia and cancer (Skalkidou 2017). In relation to fertility after treatment with progesterone, some studies have shown a live birth rate between 25% and 35%; this being higher with assisted reproductive techniques (Erkanli 2010; Gallos 2012)

Discussion:-

Management of cystic endometrial hyperplasia:

Pharmacological and non-pharmacological interventions

Medical management for endometrioid endometrial cancer/atypical hyperplasia has been based on progestogens (Corzo 2018; Niwa 1997; Plaxe 2016), given orally or via a levonorgestrel-releasing intrauterine system (IUS) (Burke 2014; RCOG 2016; Sundar 2017). A few studies and case series have shown the efficacy of metformin in proliferative disorders of the endometrium (Tabrizi 2015), including atypical endometrial hyperplasia and early stage endometrial cancer (Session 2003). Other hormone treatments acting on oestrogen levels include Gonadotropin-releasing hormone (GnRH) agonists and aromatase inhibitors.

Other pharmacological interventions include drugs to reverse insulin resistance, e.g. metformin, or pharmacological interventions to promote weight loss, such as appetite suppressants or drugs to reduce fat absorption

Non-pharmacological interventions can include ‘lifestyle' interventions aimed at promoting weight loss. Their objective is to reduce nutrient intake (diet) and increase physical activity. These interventions are beyond the scope of this Cochrane Review since, alone, are unlikely to have a rapid enough effect in the presence of an otherwise untreated cancer. Interventions to promote weight loss in women conventionally treated for endometrial cancer have been reviewed elsewhere (Kitson 2018)

Surgical interventions

Bariatric, or weight loss surgery, is a treatment for morbid obesity. It is the only treatment for obesity shown to deliver definitive weight loss at long-term follow-up (Khwaja 2010). In addition to weight reduction, there is a high rate of improvement or even cure of co-morbidities associated with obesity, such as Type II diabetes mellitus, obstructive sleep apnoea, hypertension, asthma, osteoarthritis, cancer-risk and gastro-oesophageal reflux disease

(Adams 2009; Upala 2015). Techniques include: Roux-en-Y gastric bypass; adjustable gastric band and sleeve gastrectomy, normally via a laparoscopic approach. Bariatric surgery may be carried out within the framework of the primary prevention of endometrial cancer and data on bariatric surgery, as a treatment for established cancer, are limited at present.

How the intervention might work

Obesity is a major risk factor of endometrial cancer and hyperplasia. A recent meta-analysis demonstrates that the risk of endometrial cancer increases as weight increases (Jenabi 2015). In obese women there is a metabolic state that promotes oncogenesis. This metabolic state is related to hyperoestrogenaemia, inflammation and insulin resistance, and leads to multiple changes in oncogenic signalling pathways (Mackintosh 2013), providing potential targets for treatment.

Progestins and hormonal treatment

Common reasons for hyperoestrogenaemia are excessive endogenous oestrogens produced by adipose cells in obese women or chronic anovulation. The goal of hormonal treatments is to counterbalance the action of oestrogens, or reduce oestrogen levels. Progesterone has been the most widely used hormone treatment, but GnRH agonists or aromatase inhibitors have also been used.

Progesterone has an essential role in limiting the proliferative actions of oestrogens on the endometrium. Progestins have been shown to have other anti-proliferative actions including: oestrogen receptor inhibition; anti-angiogenic action; and Insulin-like growth factor 1 (IGF-1) inhibition (Kim 2013)

Endometrial hyperplasia expresses high levels of progesterone receptors (Miyamoto 2004). Low-grade endometrial cancer often expresses oestrogen and progesterone receptors (PR) (Darvishian 2004; Demopoulos 1999). PR-negative tumours do not respond to treatment with progestins, although PR expression alone does not guarantee response to treatment, since less than a half of women will demonstrate a sustained response. From studies of progesterone treatment for endometrial cancer, complete response rates of 48% to 87% and recurrence rates of 20% to 47% have been reported (Erkanli 2010; Gallos 2012; Gunderson 2012; Ushijima 2007; Wei 2017).

GnRH agonists decrease the concentration of estrogens by decreasing the release of Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) Aromatase inhibitors block the production of estrogens in peripheral adipose tissue

Reversal of insulin resistance

Insulin resistance and hyperinsulinaemia are key factors in endometrial hyperplasia and can be factors in the initiation of endometrial cancer (Shan 2014). Interventions that work by reversing insulin resistance include pharmacological and non-pharmacological management (including weight-loss surgery).

Metformin is an anti-diabetic drug that regulates glucose metabolism. Metformin has multiple anti-proliferative mechanisms, including: reduction of insulin and IGF-1 levels (Ferguson 2013; Kim 2013; Wang 2012); increase of progesterone receptor expression; and reduction of progesterone resistance (Xie 2011). Results of a meta-analysis suggests that metformin is useful in the reversal of proliferation biomarkers related to tumour progression, and can lead to reversal of atypical hyperplasia or improvement in survival of endometrial cancer (Meireles 2017).

Weight loss interventions (lifestyle interventions) in obese women at risk of endometrial cancer produce changes in blood biomarkers associated to endometrial cancer (Yates 2017). Breast cancer can be hormonally-driven, in the same way as endometrial cancer. In breast cancer, weight loss interventions decrease oestradiol levels (total and free) (Rock 2013). These interventions, alone or in combination with metformin (Patterson 2018) can reduce recurrence and mortality rates.

A meta-analysis that evaluated the relationship between body mass index (BMI) and mortality in endometrial cancer showed that increased BMI is associated with increased mortality (Secord 2016). Weight-loss interventions may improve the survival in women with endometrial cancer or atypical hyperplasia through pathways that link obesity and endometrial cancer.

Observational evidence links intentional surgical weight loss with reductions in endometrial cancer incidence (Anveden 2017; Luo 2017). A recent review on bariatric surgery to prevent endometrial cancer development concluded that "bariatric surgery seems to reduce the risk of endometrial cancer" (Winder 2018).

However, there is a dearth of evidence on the effect of weight-loss interventions on women with established endometrial cancer, as shown in a recent Cochrane Review that failed to identify randomized controlled trial (RCT)-level evidence for assessing the effect bariatric surgery on women with endometrial cancer following conventional treatment (Kitson 2018).

Our case summary:
37 years old para 2 from previous marriage,LCB:10 YEARS, presented with irregular heavy vaginal bleeding , with chronic pelvic pain since 3 years, asking for infertility management, as she got second marriage since 3 years, by detailed history, physical examination, laboratory and radiological investigations diagnosed as atypical endometrial hyperplasia, opted for fertility preserving medical management with hormonal IUS plus oral progesterone , and close observation and follow up 6 months, followed by removal of IUS, oral progesterone , spontaneous pregnancy, which was full eventful pregnancy ended by emergency lscs at 39w, full term living baby 3.5 kg.

Case presentation
Personal History:
37 years old, para 2, previous 2 normal deliveries from previous marriage, second marriage since 3 years, came to the clinic c/o of irregular heavy bleeding, pelvic pain, asking for infertility management as she was known case of bilateral PCOS

Medical Past History:
Known case of PCOS, GDM in previous 2 pregnancies, mild smoker, ectopic pregnancy managed medically.
Surgical:
- Bariatric surgery 18 months back,
- Electrocautry MAZ for cardiac arrhythmia 4 years ago

Family History:
- Father has DM, mother has Brain tumour, grandmother has cancer thyroid

Physical Examination:
- Bulky uterus, with sub serous fibroid 4.7x3.2 cm.
- Endometrial thickness 1.3 cm, cervix hypertrophic with multiple nabothian cysts, bilateral PCOS, tender cervical motion.
- HB:9.9gm/dl
- Pap smear: moderate inflammatory reaction.

Initial management:
- Patient received medical treatment for cervicitis and abnormal uterine bleeding
- No response, after 2 days came with sever vaginal bleeding in spite of medical treatment
- Emergency admission for hysteroscopy, endometrial sampling done for HPE, hormonal IUS inserted at same time
- Report of HPE : atypical endometrial hyperplasia??
- Patient and her husband councelled about risk of progression to endometrial cancer 23%, hysterectomy as first line treatment
- Both Partners asking for fertility preserving management by progesterone.

Medical Management:
- Patient offered oral progesterone tablet + mirena as high progestogens
- Patient advised for regular endometrial sampling every 3 months, attend ED if excess bleeding, she was complaint, endometrial sample collected by pipple curette after 3 months, no hyperplastic cells detected

Follow up:
- After 6 months, asked to remove hormonal IUS , to get pregnant.???

- Detailed counselling about risk of recurrence and progression to cancer endometrium,
- After removal of IUS?what's next?

Natural conception versus ART:
- patient offered duphaston 10 mg pobd for 20 days, to prevent irregular bleeding, and improve chances of natural conception.
- After 20 days has +ve urine pt at home

Serial B HCG:
- B HCG: 72.85
- AFTER 48 HOURS:166.7
- After 48 hours:561.5
- After 4 days:3727
- Tvuss confirm IUGS, no Fetal pole, for follow up
- After one week IUGS 6w, FHR+ve
- NOW YOU ARE PREGNANT.

Risk factors in pregnancy:
- PCOS,AEH?
- Fibroid with degenerative changes, red degeneration
- Iron deficiency anemia
- Personal H/O GDM
- Migraine
- H/O Smoking
- Supine hypertension syndrome, recurrent collapse
- Sciatica
- Thrombo prophylaxis versus bleeding risk
- Threatened abortion, placental abruption at 21 weeks

Hospital Admissions:
- ICU Admission: three times, first at 21 weeks, placental abruption supine hypotension syndrome
- Second: supine hypotension syndrome at 29w
- third: supine hypotension with sever sciatica at 33 weeks.
- 7 admissions to ward with:
- Sever hyperemesis, threatened abortion, acute abdominal pain with degenerated fibroid, supine hypotension????

Delivery:
- Regular follow up in OPD weekly, till 39 weeks, she has irregular labor pains, not progressing, emergency lscs done, single active female fetus 3.5 kgm with good Apgar sore at 16/5/2022
- Uneventful perperium
- Post natal follow up of atypical endometrial hyperplasia and fibroid:
- Assessment of fibroid and endometrial thickness after 6 weeks postpartum, fibroid 6x5 cm, advised for laparoscopic myomectomy post menstrual?'
- Endometrial sample collected by pipplecurrete to role out recurrence of endometrial hyperplasia, secretory endometrium under effect of progesterone??
- BHCG: 6221 at 18/8/2022???
- Unfortunately,this pregnancy became missed at 10 weeks, followed by surgical evacuation of missed abortion after failure of conservative management

Patient inserted Hormonal IUS again post abortive with regular endometrial sample by pipple cannula every three months, were negative.

6 months post abortive,laparoscopic myomectomy done with preserved IUS in place

After 18 months of Mirena insertion, she asked to remove the IUS for natural conception again, she continued on duphaston 10 mg pobd continuous, she got another natural pregnancy after three months of duphaston and Glucophage with wt reduction,

Pregnancy was complicated by gestation diabetes controlled by diet and Glucophage 1500 mg po od, At 39 weeks Opted for elective lscs,single term female baby wt 3.4 kgm.

Advised for hysterectomy to reduce the risk of endometrial cancer but, she is still willing for fertility preservation, thus performed IUS insertion and regular endometrial biopsy by pipplecurrete.

Conclusion:-

- Fertlity preservative management for atypical endometrial hyperplasia still promising option for young age women with:
- Life style modification
- Wt loss
- Metformin to revert insulin resistance
- Hormonal progesterone(Hormonal IUS and oral progesterone)
- Regular follow up and endometrial sampling.
- Inspite of high doses of progesterone with each pregnancy still risk of endometrial cancer present and patient advised for cesarean hysterectomy for next pregnancy.

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