Levonorgestrel Releasing IUS (Metraplant E) in the Management of Copper IUD Related Heavy Painful Menstrual Loss

Thesis

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By

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Contents

List of Abbreviations

%..... Percent

°C ..... Celsius

µg ..... Microgram

AR..... Androgen receptor

BBT..... Basal Body Temperature

BTB..... breakthrough bleeding

BV ..... Bacterial vaginosis

Cm ..... Centimeter

COC..... Combined oral contraceptives

Conc..... Concentration

DMPA..... Depot MedroxyProgesterone Acetate

e.g..... for example

E2..... Estradiol

EC ..... Emergency contraception

EH..... Endometrial hyperplasia

ER ..... Estrogen receptors

ERT ..... Estrogen replacement therapy

EVA ..... Ethelene Vinyl Acetate

FAM..... Fertility Awareness Methods

FDA ..... Food and Drug Administration

Fig..... Figure

FSH..... Follicle Stimulating Hormone

GdA ..... Glycodelin A

GnRH ..... Gonadotropin releasing hormone

HB..... Hemoglobin

HESCs ..... Human Endometrial Stromal Cells

HIV ..... Human immunodefiency virus

HRT..... Hormone replacement therapy

IGF..... Insulin-like growth factor

IGFBP ..... Insulin-like growth factor binding protein

IUCD ..... Intrauterine contraceptive Device

IUD ..... Intrauterine Device

IVR ..... Intravaginal ring

Kg..... Kilogram

LARC ..... Long-acting reversible method of contraception

LH..... Luteinizing hormone

LNG..... Levnonorgestrel

LNG-IUS..... Levonorgestrel-releasing intrauterine system

MBL..... Menstrual blood loss

Min..... Minute

Ml..... Milliliter

Mm..... Millimeter

MPA..... Medroxyprogesterone acetate

PBAC..... Pictorial Blood loss Assessment Chart

PDMS ..... Poly dimethyl Siloxane

pg ..... Picogram

PID..... Pelvic Inflammatory Disease

PIP ..... Progestasert Intrauterine Progesterone

PMS ..... Premenstrual syndrome

PR ..... Progesterone receptors

PVC ..... Poly Vinyl Chlorid

SERM ..... Selective Estrogen Receptor Modulator

SSR ..... Stainless Steel Ring

STD..... Sexual Transmitted Disease

UK..... United Kingdom

US..... United States

VMS..... Verbal Multidimensional Scorning System

WHO ..... World Health Organization

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Introduction

Intrauterine methods of contraception (IUC) include the copper intrauterine device Cu-IUD and the Levonorgestrel releasing intrauterine systems LNG-IUS. IUC is considered to be a long acting reversible method of contraception (LARC).

The IUD is the most commonly used method of reversible contraception worldwide, and is used by an average of 23 percent of female contraceptive users, with a range of <2 to >40 percent depending on the country ***(Buhling , et al., 2014)*** .

In 2014, IUDs were used by 27 percent of female contraceptive users in Asia and 17 percent of female contraceptive users in Europe . Use of IUDs has increased in the United States (US): In the decade from 2002 to 2012, IUD use rose from 2 to nearly 12 percent among US women using contraception. ***(Finer* et al., *2015).***

Actively informing women about benefits, risks, and common side effects of IUDs appears to improve consideration and acceptance of the method ***(Harper* et al., *2015).***

The most common reasons for the discontinuation of this method are menstrual bleeding and dysmenorrhea. In the first year of use between 4% and 15% of women using acopper IUD will have it removed for these reasons. ***(Speroff et al., 2006).***

Side effect and risks

Bleeding pattern

The most common causes for discontinuation of IUC are pain and menstrual bleeding patterns. ***(Grunloh,…et al.2013.)***

The copper IUC is associated with increased menstrual flow both in length of menses and in amount of blood loss. A prospective study of over 1900 Copper T380A users found that many side effects related to bleeding and pain decreased over time. ***{El-Hefnawy,…et.,al 2008.}***

However, most of the improvement was in symptoms occurring during menses, whereas most intermenstrual complaints (such as unscheduled bleeding) did not decrease with time. We remove the IUC if the woman complains of menorrhagia and experiences a clinically significant fall in hemoglobin. These patients may consider another method of contraception or insertion of a LNg IUC since the mean per cycle blood loss for the LNg IUC is 5 mL versus 55 mL for the copper IUC . ***[Milson,et al., 1995]***

The LNg IUC is associated with a reduction in menstrual blood loss; LNg IUC users report fewer bleeding or spotting days per month compared with noncontraceptors and users of copper IUCs . However, many LNg IUC users experience episodes of unscheduled bleeding, which may be limited to spotting. The incidence of unpredictable bleeding is greatest in the initial six months of use, although episodes may occur throughout usage. The proportion of users with amenorrhea increases with duration of use. **[Mercorio,…et al., 2003]**

At six months of use, 44 percent of users have amenorrhea, 25 percent experience oligomenorrhea, and 25 percent experience unscheduled spotting; the remainder has either normal or heavy bleeding. At 24 months of use, 50 percent have amenorrhea, 25 percent have oligomenorrhea, and 11 percent have spotting; again the remainder report either normal or heavy bleeding. ***[Hidalgo, …et al.,2002].***

Amenorrhea in LNg IUC users is due to endometrial decidualization and atrophy; at one year, the majority of women have ovulatory cycles. ***[Rönnerdag, et al., 1999] .***

The decrease in uterine bleeding that occurs in most LNg IUC users is associated with a corresponding increase in hemoglobin levels. [**Sivin, et al., 1994 –Azzam, et., al., 2006]**

Changes in bleeding patterns, primarily unscheduled spotting and bleeding and prolonged bleeding episodes, are the main reasons for premature LNg IUC removal. Some early studies reported amenorrhea was the principal cause for removal, but subsequent studies found that amenorrhea was associated with continuation; this change may reflect improved counseling about expected changes in bleeding patterns. **[Backman,et al., 2000].**

Dysmenorrhea

Dysmenorrhea or painful menstruation is a common gynecological problem which is experienced by 40-70% of all women during their fertile life, 5-20% of whom experience severe pain which reduces their ability in participating in routine activities. Some studies have shown that 10-24% of women who suffered from dysmenorrhea asserted that symptoms interfered with their usual activities.[Cunningham &Leveno . 2010]

Fifty one percent of those who experienced dysmenorrhea symptoms expressed that these symptoms prevent them from taking apart in their job or their school. The conventional treatment of primary dysmenorrhea is based on the prevention of prostaglandin production using non-steroid anti-inflammatory drugs or by preventing ovulation and reducing prostaglandin levels by the use of oral contraceptive pills [Morrow & Naumburg 2009]

Copper IUD is a conventional contraceptive method but due to the complications such as dysmenorrhea and hyper menorrhea, 15%- 30% of women request for its removal.**[Jiménez , ….et al., 2008]**

The levonorgestrel-releasing IUD has been successfully used in primary and secondary dysmenorrhea by suppressing endometrial prostaglandin synthesis. **[Lethaby & CookeI 2005]**

In addition, the levonorgestrel IUD is especially effective in treating dysmenorrhea caused by adenomyosis and recto vaginal endometriosis, which is associated with severe dysmenorrhea, dysparunia and pelvic pain

[Bragheto, et..al., 2007]

The mechanism of levonorgestrel-releasing IUD is to decrease pelvic pain by releasing 20 µg levo norgestrel locally in the uterine cavity every day, which is more effective than oral therapies.**[Thonneau & Almont 2008]**

In addition to its therapeutic role in decreasing dysmenorrhea and severe bleeding during menstruation, the levonorgestrel IUS is also used as a means of contraception. **[Gupta & Singh 2007]**

The therapeutic effects of levonorgestrel-releasing IUS on dysmenorrhea, menorrhagia, and contraception have been confirmed in different clinical trials in many countries. **[Thonneau & Almont 2008 –Azzam …et,.al,. 2006]**

Ectopic pregnancy

Women using IUD should be informed that their overall risk of ectopic pregnancy is much reduced compared with women who are using no contraception. The risk of ectopic pregnancy for 52 mg LNG-IUS users has been reported as 0.01 per 100 women years (95% CI 0.00–0.003) and 0.07 per 100 women years 95% CI 0.02–1.78) for Cu-IUD users.***[Heinemann , and Moehner 2013]***

Perforation

Overall the perforation rates with IUC are low with reported rates of up to two perforations per 1000 insertions.Factors associated with an increased risk of perforation have been reported to include relative inexperience of the clinician inserting the IUC, breastfeeding and being less than 6 monts postpartum, fewer pregnancies and more abortions.**[Heinemann ,.et al., 2014]**

Expulsion

It is reported that 1 in 20 IUC devices will be expelled and that this is most likely to happen in the first 3 months after insertion.[1] In general, similar expulsion rates are reported for both the Cu-IUD and LNG-IUS.

Retrospective studies have reported that the risk of Cu-IUD expulsion (but not LNG-IUS) is higher amongst nulliparous compared to parousv women.

[***Garbers ,….et al., 2013]***

Infection

The overall risk of pelvic inflammatory disease (PID) following insertion of IUC is low. A large retrospective cohort study found the risk of PID within the first 90 days of fitting was 0.54%. However, PID is more likely immediately following insertion; six fold increased risk in the first 3 weeks.

(Sufrin, ….et al.,2012)

Metraplant, Metraplant E, Mierna,Skyla and Femilis are variable forms of hormone releasing IUSD.

The main problem with **Metraplant** is that the hormone reservoir(s) contain silicone and levonorgestrel. Silicone manufacturing is more difficult and machines need to produce it are commercially more expensive. The use of another co-polymer **(Ethylene Vinyl acetate = EVA)** is decided as it has many of the properties of Silicone and easier to be obtained and manufactured **(Azzam, 2012)**

The most notable Advantage for **Metraplant-E** more than other LNG-IUS like Mirena, is that Metraplant-E made of EVA instead of polymethylsiloxane used in Mirena. EVA are remarkably biocompatible and have also been used in the design of biomaterials and drug delivery systems.