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Review Article

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A Literature Review Comparing Combined Oral Contraceptive Pill use and Mirena during Perimenopause

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Abstract

Introduction: Perimenopause is the period that heralds menopause and is an alternative countenance of "menopausal transition." As the median maternal age is increasing a substantial number of women in the age group of 40 – 49 may encounter unexpected pregnancies. It is well known that the risk of miscarriages is high due to poor oocyte quality. Older age women who get pregnant are at increased risk of gestational diabetes mellitus, pre-eclampsia, preterm labor, chromosomal abnormalities, cesarean delivery, and stillbirths apart from neonatal morbidities including intrauterine growth restrictions, low Apgar score, admission to intensive care, and autism.

Besides safe contraception, there are several conditions in this age group that could be treated with the use of hormonal contraceptives, including abnormal heavy menstrual cycle, vasomotor symptoms and bone loss, endometrial hyperplasia, and prevention of certain cancers.

Objective: Our review aimed to evaluate the benefits and risks of the two main contraceptives in this age group combined oral contraceptive pills and the Mirena intrauterine device. Whereas prior reviews have mainly focussed on all the contraceptive options in this age group, our focus was to compare the benefits and risks of the two main hormonal contraceptives, both of which also aid in reducing heavy menstrual loss common during this period.

Data Synthesis: We searched MEDLINE using PubMed, EMBASE, GOOGLE SCHOLAR, and Proquest for English-language articles on contraception in older women. Our methodology involved a review of the published literature from mainly 2012 to the end of June 2022. We also reviewed the statements and clinical practice guidelines from the US Centers for Disease Control and Prevention and the Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists.

Conclusion: No method of contraception is contraindicated by age alone, although combined hormonal contraception is generally not recommended for women over 50 years. The intrauterine system has specific benefits in perimenopausal women as a low-dose method of effective hormonal contraception, which also helps manage heavy menstrual bleeding and endometrial protection in women necessitating estrogen replacement. It has no contraindications for use in women with comorbidities in this age group, such as cardiovascular risk factors, venous thromboembolism, hypertension, or stroke. The US and UK medical eligibility criteria also favor using progestin-only contraceptive methods for common medical conditions. Although it does not benefit vasomotor symptoms, it can be used with low-dose estrogens in women with an intact uterus as hormone replacement therapy with contraception.

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Introduction

The period that indicates the onset of menopause is defined as perimenopause or "menopausal change." It usually starts around 40, 5-10 years prior to menopause[2].

According to the Stages of Reproductive Aging Workshop (STRAW+10 Staging System) [1], early perimenopause commences with irregular or "unpredictable length" cycles with at least 7-day variations in cycle length between repeated cycles or varying cycle lengths of less than 25 days or greater than 35 days. A cycle over 60 days is late perimenopause[3].

The rate of fertility declines with age and though perimenopausal women are less likely to become pregnant, yet they still need safe and successful contraception. A Canadian census showed that 15% of the women who got pregnant were 40-49 years[4]. Similarly, the National Survey of Sexual Attitudes and Lifestyles (NATSAL) in 2013 showed that 20 percent happened at age 40 or older, out of which 28% ended in termination[5]. It is also well known that the risk of miscarriages is high due to poor oocyte quality. Older pregnant women are at increased risk of gestational diabetes, pre-eclampsia, preterm labor, chromosomal anomalies, cesarean delivery, stillbirths, reduced intrauterine growth, reduced Apgar, intensive care, admission, and autism[6].

The usual menopause age is around 51[6]. Still, the American College of Obstetricians and Gynaecologists (ACOG) commends the continuation of contraception up to 50-55 in women[7]. No contraceptive method is contraindicated based on age only. The 2018 WHO family planning recommendations stated that women over 40 without co-morbidities could use combined pills[8].

Objective:

Whereas prior reviews have mainly focussed on all the contraceptive options in this age group, our main focus was to compare the benefits and risks of the two main hormonal contraceptives, both of which also aid in reducing heavy menstrual loss common during this period.

Data Synthesis:

We searched PubMed, EMBASE, GOOGLE SCHOLAR, and Proquest for articles on contraception in older women. mainly from 2012 till June 2022. The statements and clinical practice guidelines from the US Centers for Disease Control and Prevention (CDC), the Faculty of Sexual and Reproductive Healthcare (FSRH), and the Royal College of Obstetricians and Gynaecologists were also reviewed. Keywords for the search included -Contraception, Perimenopause, Combined oral contraceptive pills, Levonorgestrel Mirena device, Risks, and Benefits.

Inclusion criteria primarily but not exclusively were peer-reviewed studies that discussed the advantages and disadvantages of each of these methods in this age group specifically. Papers were excluded if they- 1) focused on younger age groups, 2) women with breast and other cancers,3) did not present original findings (letters to the editor or opinions), 4) conference abstracts, and 5) in other than English.

World Health Organization (WHO) describes copper devices, progesterone IUDs, implants, and sterilization as the "highest rank methods" concerning efficiency[8] with a failure rate of less than 1% during the first year of use.

In perimenopausal women until one-year post menopause, the combined oral contraceptive pill (COC) is a safe option now, provided the women don't have co-morbidities like hypertension, hyperlipidemia, or heart diseases. CDC states that the only age-related risk for combined pills is for women above age 35 and heavy smokers (>15 daily)[9].

Combined Oral Contraceptives (COC) and Heavy Menstrual Loss

COC is highly effective in this age group, as they inhibit ovulation, and the failure rate is less than 1 percent[9].

Many women in this age group suffer from menstrual cycle changes from shorter cycles to excessive bleeding and irregular cycles with premenstrual spotting. COCs can reduce menstrual loss by up to 40% and reduce menstrual cramps [11]. For perimenopausal women, COC's use offers potential additional benefits beyond contraception, evading abnormal periods, regulating menstrual bleeds and further eliminating pelvic pain and dysmenorrhea[10].

The 30-35 ug Ethinyl oestradiol COC is more effective for the combined effect of contraception and effective reduction in the menstrual cycle. U.S. Food and Drug Administration (FDA) has commended an oestradiol/dienogest combination as an effective contraceptive that reduces menstrual flow in this group[12]. The anti-androgenic and progestin effect of dienogest, with mild estrogenic activity (2mg Estradiol Valerate), is a contraceptive method that helps counteract the negative changes in the body counter occurring in these women[13].

Lng Ius and Heavy Menstrual Loss:

Levonorgestrel-releasing intrauterine was introduced in Finland in 1990 [56]. Mirena, LNG-IUS, includes 52 mg of levonorgestrel and releases a daily dose of 20 mcg in the uterine cavity for five years. The other levonorgestrel-releasing intrauterine systems will not be discussed in this review.

LNG-IUS has established uses in other conditions, such as reducing dysmenorrhea, the control of heavy periods,

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and treating and preventing endometrial hyperplasia, and is licensed for these non-contraceptive uses[62]. Bitzer et al. reported a mean reduction in blood loss of more than 70% in the initial three months of LNG-IUS insertion in their review[63]. A study by Yoo et al. [64] evaluated the risk factors for hysterectomy and its rate during the first two years of use of an LNG IUS for women above forty. A success rate of 80.7% was noticed among partakers who continued with the LNG-IUS method for 2 years. LNG-IUS is also beneficial for the treatment of adenomyosis and endometriosis.

COC and Fibroids

An RCT comparing the effects of COCs and LNG IUS for treating fibroids in women with menorrhagia showed LNG-IUS to be superior although COCs did show a substantial decrease in menstrual bleeding with no change in fibroids volume[65].

Moorani et al. in their systematic review showed that LNG-IUS were better than COCs in managing heavy menstruation, and hemoglobin concentration. They concluded that evidence to use COCs for treating women with symptomatic fibroids needs revision[66].

LNG IUS and Fibroids

A decrease in menstrual bleeding in women with fibroids by producing endometrial atrophy occurs with LNG IUS[60]. This reduced menstrual loss, corrects anemia, and increases hematocrit levels. There is a high risk of device expulsion, especially in cases of multiple fibroids[61]. A prospective observational study by Machado et al. [77] to determine the ratio of avoidance of hysterectomy in perimenopausal women with fibroids who used LNG-IUS to an earlier need of surgery and comparing patients' satisfaction with both treatments concluded a decrease in the number of hysterectomies in women with uterine fibroids with greater satisfaction in the LNG IUS cohort.

COC and Premenstrual, Vasomotor Symptoms

Vasomotor symptoms are present in 70 to 80 percent of perimenopausal women[14]. The European Union (EU) has effectively approved using the combined pill in women with climacteric symptoms as well to reduce the incidence of premenstrual syndrome and menstrual-related headaches in these women[13].

An observational study of 3 years concluded that 90 percent of perimenopausal women had relief by taking COC[15].

LNG IUS and Vasomotor Symptoms

There is no support for the beneficial effects of the LNG IUS in reducing vasomotor symptoms in literature though it has been effectively used with estrogen. Wildemeersch (2016) concluded that from perimenopause through menopause and into post-menopause, offering gel, patches, or oral estrogens for vasomotor symptoms along with LNG IUS prevented endometrial proliferation and effectively treated abnormal heavy uterine bleeding and hyperplasia with added contraceptive benefits[78].

COC and Prevention of Cancers:

Ovarian Cancer

Many broad pooled studies encourage COCs use to protect against ovarian cancer risk, with a 50% risk decline with longer usage[17,18]. The protective effect against epithelial ovarian cancer is diminished by 20 percent after five years of COC, use and even later[16]. The mechanism of diminished tubal motility and secretion, inhibition of ovulation, decreased menstruation, and atrophy of the endometrial glands associated with COCs might be responsible for hampering the carcinogenic pathway.

A total of 200,000 predicted ovarian cancers and 100,000 fatalities prevented by COC use have been reported in a recent pooled analysis of ovarian cancer globally[19]. The degree of the protective effect and the duration of COC use is correlated.

Carriers of BRCA1 and BRCA2

A recent meta-analysis of 18 comparative, reflective studies of COC use in BRCA 1/2 mutation carriers established that users of COC were relatively at a reduced risk of ovarian malignancy, though no variation between mutation groups was noted[20]. An extended use period ensued in higher protective power. A 2021 cohort also supported this effect[21]. COC use also seems to be associated with a diminished risk of fallopian tube malignancy in the general populace[22].

Endometrial Cancer

A 30-40% reduced risk of endometrial cancer is also linked with COC use in broad epidemiological studies, and this effect begins immediately after using COC. This protective effect can still be there after the discontinuation of COC[23]. This effect is mainly through the progestogen action limiting endometrial proliferation.

Colorectal Cancer

Colorectal cancer (CRC) is a known cancer in women, with survival rates around 65%. The International Agency for Research on Cancer (IARC) has noted that a reduction in the risk of colorectal cancer may be associated with COC use. Yet, the results of epidemiological studies have not shown a consensus in many years[24].

A modest reduction in colorectal cancer by up to 15 to 18 percent has been observed in COC users compared to non-users[25].

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LNG IUS and Prevention of Benign Non-Atypical Endometrial Hyperplasia

Endometrial hyperplasia is reported to be most frequent in pre and postmenopausal women and can present with abnormal uterine bleeding[79]. The risk of atypical hyperplasia developing into endometrial cancer is 8-29%[80].

An RCT by Hashem et al[67] compared the effectiveness of oral norethisterone acetate (NET) and LNG-IUS for treating perimenopausal women with nonatypical endometrial hyperplasia. Patients received LNG-IUS or NET; 15 mg/day for three weeks/cycle for 3-6 months. The follow-ups based on outpatient endometrial biopsies undertaken at 3-, 6-, and 12-month intervals post treatment showed a substantially higher regression rate in the LNG-IUS group and a higher hysterectomy rate in the NET group compared to the LNG-IUS.

COC and Bone Mineral Density (BMD)

A one percent decline in BMD occurs each year after age 40. COC users show increased BMD in the lumbar spine, neck, and femur compared to non-users in late perimenopause[27].

A two-year longitudinal study on the effects of different low-dose COC on BMD between the ages of 40 -49 with no difference in BMI[26] compared perimenopausal women with oligomenorrhea treated with COC containing different progestins to a similar cohort of women given calcium supplements. The results showed that the low-dose COC preparations could inhibit the reduction in bone density perceived in these women. At two years the spine BMD values measured in COC-treated women were substantially elevated than those in the calcium-treated group[27].

LNG IUS and Bone Mineral Density

Although in an observational study by Lopez et al.[59], it was noted that hormonal LNG- IUS users could have reduced fracture risk however, FSRH guidelines [31] state that LNG-IUS devices did not show a decrease in bone reduction and a decrease in estradiol levels.

COC and Cardiovascular Risks

Increased blood pressure and fluid retention occur with estrogens due to increased hepatic production of angiotensin. Estrogens also raise VLDL and HDL, and reduce LDL, with enhanced liver proteins causing changes in the pro-coagulation/fibrinolytic balance[57]. The increase in estrogen levels has been associated with an enhanced risk of myocardial infarction (MI), venous thromboembolism, ischemic strokes, and prolonged QT interval[58].

The incidence of transient ischemic attacks and MI in the Danish population was 20 and 100 times more in women (45-49) than in younger women[28]. Overall stroke risk was increased by 2.2 times, and the overall risk of MI was also doubled[29].

A Cochrane review of 24 database studies also showed an increased risk of MI and thrombotic risk. They found that the relative risk of stroke and MI increased from 1.6 for 20 mcg of Ethinyl Estradiol to 2.0 for higher estrogen pills. The women in this study were 18-50 years old, and both women using and not using combined pills were included. The risk was highest in women using a tablet containing 50 mcg or more of estrogen[30]. Other risk factors such as obesity, hypertension, and thrombogenic mutations also enhance the risk of venous thromboembolism with the increase in age[33].

FSRH recommends that COC with Norethisterone or Levonorgestrel should be considered as the contraceptive for women above 40. They also recommend pills with estrogen of less than 30 mcg dose to lower the risk of cardiovascular disease and strokes[31].Thromboembolism risk with COC is further increased in women with genetic thrombophilia, and the risk increases more with 3rd generation of progesterone and is lowest with Levonorgestrel[32,34].

LNG IUS and Cardiovascular Risks

As progesterone differs from estrogens in first-pass metabolism rate formulations thus, they can be used safely in women with higher cardiovascular or thrombotic risk[68].

Currently, the available data suggest that there is barely any risk of VTE linked to progesterone contraception. No increase in myocardial infarction (MI) was noted with the use of progesterone contraception in the meta-analysis[69]. Although, studies on cardiovascular risk factors, are supportive but more research is required, especially in higher-risk women[70]. For women with either multiple risk factors for stroke, a history of ischaemic heart disease, or a history of VTE, the benefits of initiating an LNG-IUS generally offset the risks (UKMEC 2).

COC and Breast Cancer Risk

The ACOG Practice Advisory has reconfirmed its advice in the critical points (January 2022) that there is an 8-24% rise in the risk of breast cancer (BC) associated with COC use[35].

Inherent estrogens are considered mutagens causing a gene-damaging mechanism[36]. The estrogens are speculated to cause the activation of polycyclic aromatic hydrocarbons, which eventually cause gene damage.

Research on increased breast cancer among women with COCs has always shown opposing results: from no rise in risk to a 20%–30% surge. The research of the Nurses' Health, RCGP (Royal College of General Physicians), and Oxford Family Planning Association are 3 extensive studies that indicate that neither ongoing past COC use nor current use was related to a higher BC risk[37,38,39]. In a case-control study, which consisted of more than 4500 women with breast cancer, the risk was not suggestively different between current or prior COC users[40].

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Conversely, the Morch et al. prospective cohort study and the Collaborative Group Metanalysis Study have projected a relationship between the use of COC use and BC [41,42,43]. The Collaborative Group on Hormonal Factors in Breast Cancer in their meta-analyses observed that the use of COC use was linked to an increased risk of BC which was reduced later when COC was discontinued and finished after ten or more years[44].

Another big prospective cohort study of women from a Danish registry followed up to eleven years demonstrated that present or late COC users showed a higher risk of BC than women who never used COC and this rose with the duration of use but not significantly[45].

The results of the Nurses' Health Study, which is the most recent significant study[46] stated an increased death due to BC in women who used COCs for five years or more compared to women who never used COCs. It also stated an increased risk for current users than for women who never use it. Another recent meta-analysis of COC use and breast cancer risk supported a sizable direct link with a 0.7% increased risk reported with each year of age[47].

With no agreement on whether BC is linked with COC use, it is advisable to practice caution. However, breast cancers diagnosed with COC were less clinically advanced than in other women who never used COC[48].

Women with a Family History of Breast Cancer

In women with a family history of BC, COC was not linked to increased breast cancer, nor did the risk alter with different COC formulations and BRCA gene carriers[49]. Literature [48,50,52,53] does not show an increased risk for breast cancer among women with either a family history or susceptible genes of BC. Hence, women with breast cancer sensitivity genes (such as BRCA) or a family history of BC can use COCs at least for a short duration.

UKMEC does not advise the use of COC in women with existing BC and considers it as category 3 in women with the prior disease with no evidence of disease for five years) [34]. However, in a study by Moorman et al.[51], the use of COC among BRCA1 and BRCA2 mutation carriers demonstrated a higher relationship with BC though not significant.

LNG-IUS and The Risk of Breast Cancer

The FSRH Guidelines do not support a link between breast cancer and LNG-IUS.[31]. A recent systematic review of the risk of breast cancer in LNG-IUS users was published in March 2023[72] concluded no evidence of elevated risk of BC in LNG-IUS.

A Cochrane Review reported that in BC patients using tamoxifen, the insertion of LNG-IUS over one year showed a decline in the risk of developing endometrial polyps though more studies are needed to start the use of LNG-IUS in these women[71]. Larger studies are required to evaluate and determine whether the LNG-IUS might impact the risk of secondary BC as there is no clear consensus from the literature[71].

UKEMC states that the risk of LNG-IUS users in women with active BC is not acceptable. In contrast, it is category 3 (risks outweigh benefits) for a woman who had BC in the last five years with no recent recurrence. There is no contraindication for its use in high-risk women, with a family history of BC or BRCA1 gene carriers.

COC and Risk of impaired glucose tolerance or Type 2 Diabetes:

In a study in Finland, a survey was given to women at age 46 and they underwent an oral glucose tolerance test between 2012 and 2014. They were evaluated as current COC, progesterone-only, and nonhormonal contraceptive consumers. It concluded that current COC users were notably linked with prediabetes and type 2 diabetes compared to others. After five years of usage the prediabetes risk amplified to 2.2-fold, and the type 2 diabetes risk rose to 4.5-fold. This study concluded that COC use in perimenopausal women was associated with a significantly increased risk of hyperglycemia[54].

LNG-IUS and Type 2 Diabetes

LNG-IUS has demonstrated beneficial effects in conditions like diabetes. Studies from an RCT of women with uncomplicated diabetes mellitus receiving either copper IUD or LNG-IUS had glucose levels measured over 12 months of device use. It concluded that LNG-IUS was not linked with any harmful impacts on glucose metabolism[73].

COC and Risk of Hypertension

COC enhances hypertension risk, and women in the perimenopausal group may also have other cardiac risks. A recent meta-analysis established a link between the duration of oral contraceptive use and the risk of hypertension with a direct relationship found with duration;13% for each 5-year addition in COC use[55].

LNG IUS and Risks of Hypertension

The use of LNG IUS was associated with decreased systolic blood pressure use in a systematic review and meta-analysis comparing the risk of hypertension, and changes in blood pressure in COC and LNG IUS[74].

Undesirable Side Effects of LNG IUS

Weight gain has been commonly noted in LNG-IUS users, but no substantial variance between hormonal and non-hormonal IUS has been noticed[75].

Irregular bleeding and amenorrhoea and scanty bleeding are frequent yet certain women will have normal bleeding patterns and others may encounter prolonged and more

frequent bleeding. Bleeding patterns in LNG-IUS users usually get better with time after insertion (>3 months). Irregular bleeding may persist in around 20% of women at one year of use[31].

LNG-IUS could have other side effects, such as acne, breast tenderness/pain, headache, and mood changes[50]. An increased risk of benign functional ovarian cysts has been noted in users of LNG IUS. Most of these cysts are asymptomatic and settle naturally[76].

Contraception age limit

FSRH supports using LNG-IUS until age 55 if inserted at or over 45 years. Contrary to this, it recommends that women over 50 stop taking COC and look for alternatives. The FSRH Guidelines do not support a link between BC and LNG-IUS[31].

Conclusion

No method of contraception is contraindicated by age alone, although COC is not recommended for women over 50 years. The LNG IUS has specific benefits in perimenopausal women as effective hormonal contraception, which also helps manage heavy cycles and endometrial protection in women necessitating estrogen replacement. It has no contraindications for use in women with comorbidities in this age group, such as cardiovascular risk factors, venous thromboembolism, hypertension, or stroke. There is no benefit to vasomotor symptoms but is beneficial with low-dose estrogens in women with a uterus as hormone replacement therapy and contraception.

Contributions

RJ was the lead author of the project. RJ, ASK, KI, and MSK were all involved in drafting one or multiple sections of the review paper. RJ and ASK were involved in the creation and design of tables and figures. RJ, ASK, KI, and MSK were involved in editing the manuscript and provided intellectual contributions. RJ, KI, and MSK were involved in the review and provided expert feedback on the content. All authors read and approved the final manuscript.

Conflict of interest

All authors confirm no conflicts of interest to disclose.

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Supplemenatry Data

Non-Contraceptive Benefits of COCP in Perimenopausal Women	Non-Contraceptive Benefits of Mirena in Perimenopausal Women
Reduction in menstrual loss [10,11]	Reduction in menstrual loss in women with fibroids [60,]
Reduction in premenstrual symptoms [11]	Reduction of heavy menstrual loss and dysmenorrhea [62,63]
Reduction in vasomotor symptoms [13,14,15]	Regression of Endometrial Hyperplasia [67,79,80]
Reduced risk of colorectal cancer [24,25]	As a Progesterone arm of hormone replacement therapy (HRT) [78]
Reduced risk of endometrial cancer [23]	
Reduced Risk of Ovarian Cancer [16,17,18,19]	
Increased Bone Mineral Density [26,27]	

Risk Factors Associated with COC in Perimenopausal Women.	Risk Factors Associated with Mirena IUD in Perimenopausal Women.
An increased risk of ischemic stroke, myocardial infarction, venous thromboembolism, and prolonged QT interval [57,58] A slight increase in the risk of breast cancer [41-44] Increased risk of glucose metabolism disorders.[54]	No evidence of an increased risk of breast cancer in LNG-IUS users. [72] No contraindications in women with a family history of breast cancer. [UKEMC] No increase in cardiovascular risk was noted with LNG IUS.[68,,70] Currently, the available data suggest that there is little or no risk of VTE associated with progestogen-only contraception. [69].
Increased risk of hypertension.[55]	No undesirable effects on hypertension or glucose metabolism [73,74]