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Review

Oral contraception for women of middle age

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ABSTRACT

Women at middle age have decreased fertility and their pregnancies are higher risk. Combined oral contraceptives (COC) are effective but confer increased risk of age-related diseases, especially cardiovascular diseases. These risks are lower, however, with progestogen-only pills (POP). Therefore, other than the levonorgestrel intrauterine device (LNG-IUD), POP are usually the first choice, even though they do often lead to bleeding problems, which are already frequent in the perimenopause. However, the main risk of COC, venous thromboembolism, seems not to be relevant in (non-hospitalized) Chinese women and perhaps also other Asian women. COC may therefore be in fact a better choice than POP for these groups. In contrast to POP and IUDs, they have a variety of benefits especially important for middle-aged women, including a large decrease of the risk of ovarian, endometrial and colorectal cancer, an improvement in bleeding irregularities, a reduction of climacteric symptoms and some protection against bone loss. Further research is needed into individualized and safe contraception that takes into account ethnicity, as well as other factors.

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Contents

1. Introduction

For the purposes of this paper, women of middle age are those either experiencing or soon to experience the perimenopause. They are aged above 35 years and are entering a final phase of reproductive life, associated with decreased fertility, bleeding problems, change in metabolic profile, an increase in age-related health risks (notably cardiovascular and cancer risks), and possible climacteric symptoms, as well as a decline in bone mineral density (BMD). These are the main issues to be considered if contraception is wanted. For several reasons, besides sterilization the best choice is usually an intrauterine device (IUD), particularly a levonorgestrel (LNG) IUD, potentially combined with oestrogen replacement. This choice and other non-oral contraceptives like implants, injectable progestogens, patches or a vaginal ring have been reviewed in detail elsewhere [1]. The present short review is focused on oral

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contraception, that is, combined oral contraceptives (COC), with ethinyl estradiol (EE) or the two new estradiol (E2)-based COC, and progestogen-only pills (POP).

2. Fertility

Many perimenopausal women believe they are no longer fertile and therefore do not use contraceptives. Although fertility is decreased and pregnancy rates are low, sexually active perimenopausal women may still conceive. Even with bleeding irregularities, some women have sporadic ovulation. If pregnancy occurs in this age group, it is often unintended and unwanted. Pregnant women over the age of 40 have high rates of induced abortion. Both COC and POP are effective in avoiding pregnancies and so the choice between them largely comes down to the age-related risks.

3. Official guidelines on hormonal contraception

For the use of any drugs, official guidelines have to be considered. Within the European Union, the European Medicines Agency (EMA) is the responsible body, through its Pharmacovigilance Risk Assessment Committee (PRAC). Since 2013 it has published several recommendations on the use of COC, with particular attention to the risk of venous thromboembolism (VTE) (press releases 11.01.13; 14.02.13; 25.07.13; 16.01.14; 14.02.14). The WHO has published its Medical Eligibility Criteria (MEC) for contraceptive use [2] and in the UK the Royal College of Obstetricians and Gynaecologists has published its own guidelines on the use of contraception by women aged over 40 years [3]. Other guidelines are available, for example from an ESHRE workshop [4]. In addition, guidelines from national health authorities like the so-called "Red letters" in Germany must be considered, especially for legal reasons. Table 1 summarizes the WHO MEC, which especially are important in relation to middle-aged women.

Table 1
WHO-Medical Eligibility Criteria (MEC) for women with age-related important cardiovascular risk factors (modified according [2]).

	COC	P/R	POP	DMPA	ETG	Cu-IUD	LNG-IUD
Age							
<18 years	1	1	2	2	1	2	2
18–40 years	1	1	1	1	1	1	1
≥40 years	2	2	1	2[a]	1	1	1
Obesity							
BMI ≥ 30	2	2	1	2	1	1	1
Smoking							
age < 35 years	2	1	1	1	1	1	1
age ≥ 35 years							
<15 cic	3	1	1	1	1	1	1
≥15 cic	4	4	1	1[a]	1	1	1
Hypertension							
systolic 140–159 or diastolic 90–99 mmHg	3	3	1	2	1	1	1
systolic > 159 mmHg or diastolic > 99 mmHg	4	4	2	3	2	1	2
including vascular diseases	3/4	3/4	2	3[a]	2	1	2
>2 cardiovascular risk factors	3/4	3/4	2	3[a]	2	1	2

COC: combined oral contraceptives, P: patch, R: vaginal ring, POP: progestogen-only pill, DMPA: depot-MPA, ETG: etonogestrel implantat, IUD: intrauterine device, LNG: levonorgestrel.
[a] Authors would recommend one higher MEC category.
MEC category:
1: method can be used in any circumstances.
2: method can be generally used.
3: use of method not recommended unless other more appropriate methods are not available or not acceptable.
4: method not to be used.

Table 2
Cardiovascular risks using COC with and without smoking comparing two age groups Incidence per 1 million women per year (modified according [7,8]).

Age	Without COC	Non-smoker with COC	Smoker with COC
Venous thromboembolism			
20–24 years	32.2	96.7	283.4
40–44 years	59.3	178.0	521.8
Myocardial infarction			
20–24 years	0.14	0.34	2.7
40–44 years	21.3	53.2	426.0
Ischaemic stroke			
20–24 years	6.0	15.1	30.3
40–44 years	16.0	40.1	80.2

4. Age-related risks of contraceptive use

The main concern about the use of COC is an increased risk of VTE. PRAC has reviewed the risk of VTE using COC (see press releases cited in previous section). PRAC concluded that "the benefits of COC continue to outweigh their risks", with the proviso that the risk factors have to be carefully considered in each individual case. Otherwise, "There is no reason for any woman to stop using her contraception". Women prescribed COC should be made aware of the risk of VTE and its signs and symptoms.

The problem relates to the large age-related increased background risk of VTE. In some countries, for middle-aged women with risk factors like a high BMI or smoking (Table 2) only COC containing levonorgestrel (LNG) are recommended. However, the studies comparing the different types of progestogens used in COC are still controversial [5]. Nevertheless, the companies producing them have been required to change the labelling and to describe the 2- to 5-fold higher risk of VTE with the use of progestogens like desogestrel, gestodene, cyproterone acetate or drospirenone compared with LNG; data on other progestogens are scarce or lacking [6]. In clinical terms, it is important to inform the woman that the risk of VTE during and directly after pregnancy is 3- to 10-fold higher than that associated with any COC.

Arterial risks like myocardial infarction and stroke are lower than the risk of VTE and, in contrast to the risk of VTE, mainly increase after the menopause, due to the lack of production of cardiovascular protective estradiol. These risks seem mostly to be an issue only in women with additional risk factors, like smoking (Table 2, and reviewed e.g. in [1]). The main issue remains the risk of VTE.

In consequence, middle-aged women who cannot or do not want to use IUDs are usually prescribed POP, since until now no increased risk of VTE has been observed with their use [9].

The risk of breast cancer rises dramatically between the ages of 40 and 50 years. However, women can be advised that any effect of COC is small, and some well designed studies have found no additional risk [10,11]. Regular gynaecological examinations combined with screening remain important. In contrast, the peak age for developing cervical cancer is 30–35 years. Using COC for more than five years can increase the risk of cervical cancer [12], but in practice this is less of a problem if women participate in the national screening programmes.

5. Non-contraceptive benefits of COC

Besides contraception there are important additional benefits of COC, summarized in Table 3. These benefits vary with duration

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