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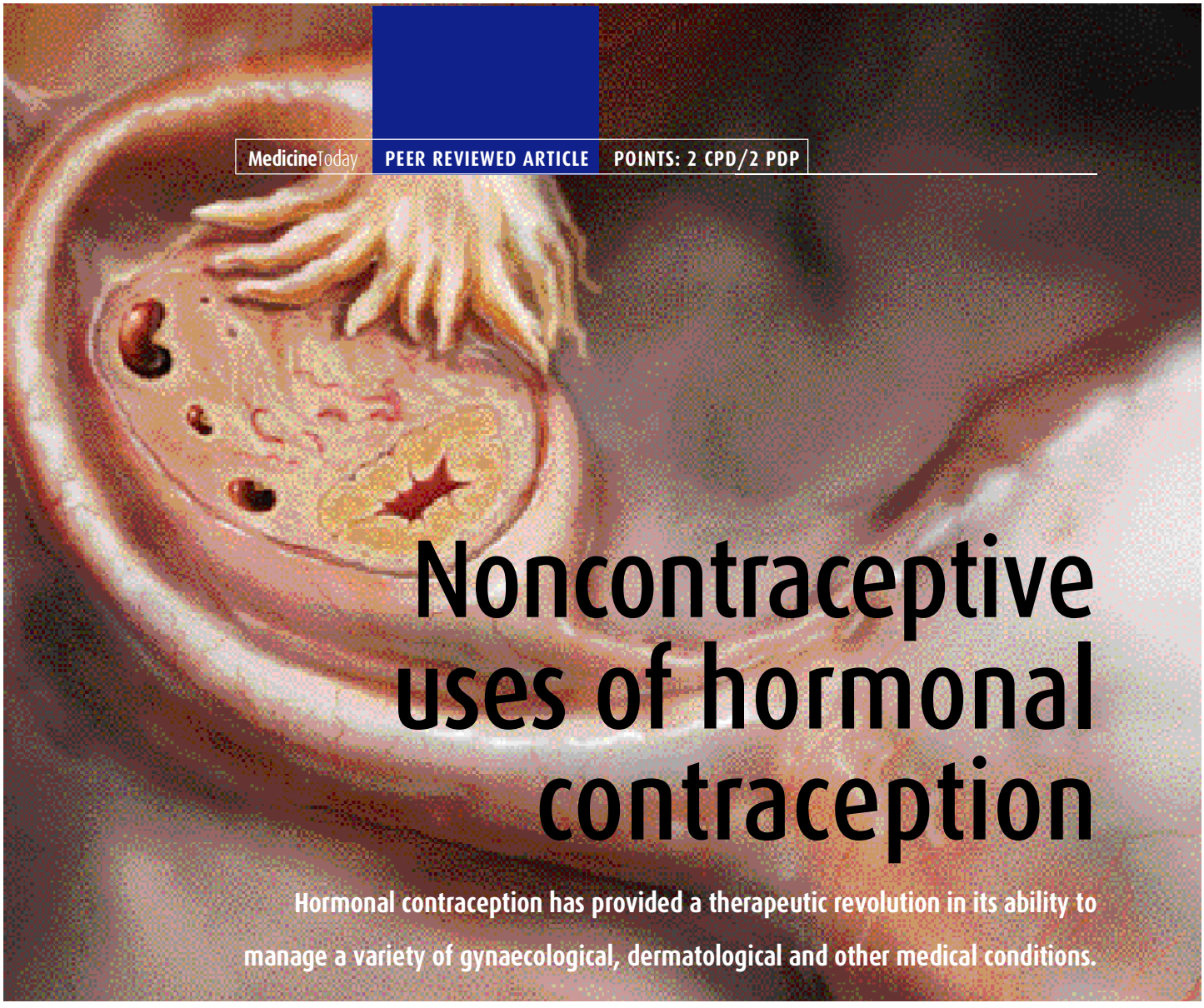

PHOTOLIBRARY

Noncontraceptive uses of hormonal contraception

Hormonal contraception has provided a therapeutic revolution in its ability to manage a variety of gynaecological, dermatological and other medical conditions.

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The combined oral contraceptive pill was the first hormonal contraceptive to be made available in Australia in 1961. Since then, it has been used as an extremely effective reversible contraceptive, and is the most popular contraceptive method in Australia.

Hormonal contraception has been nothing short of revolutionary in terms of delivery of its primary objective: efficient, safe, reversible and cost-effective fertility management. Interestingly,

IN SUMMARY

- **Hormonal contraception has important therapeutic uses beyond contraception.**
- **Hormonal contraceptives are beneficial in managing dysmenorrhoea. The levonorgestrel-containing intrauterine device, in particular, is also effective in managing menorrhagia.**
- **Use of combined hormonal oral contraceptives provides protection against ovarian and endometrial cancers.**
- **Women with androgenic conditions, such as acne and hirsutism, benefit from the use of combined hormonal oral contraceptives.**
- **Combined hormonal contraceptives are effective in inducing regular menstrual cycles and amenorrhoea.**
- **Women who have menstrual cycle-related worsening of conditions, such as epilepsy, headaches and premenstrual syndrome, may benefit from the use of hormonal contraceptives.**
- **Combined hormonal contraceptives may also be useful as hormone replacement therapy in women who are experiencing perimenopausal symptoms or with conditions such as premature ovarian failure.**

and probably somewhat unexpectedly, at least to its original developers, it has also provided a therapeutic revolution in its ability to manage a variety of gynaecological, dermatological and other medical conditions.

Doctors working at the 'coal face' have for years prescribed the pill to manage menorrhagia in women who have no further need for contraception, their partners having had a vasectomy or themselves a tubal ligation. It has also been prescribed to control acne in nonsexually active patients. Pharmaceutical companies have recently caught up with this 'noncontraceptive' use of contraceptive methods and have developed 'designer' contraceptives to further develop the range and usefulness of these products.

It has been proposed that the combined oral contraceptive pill is an important preventive tool for the most insidious of neoplasms, ovarian cancer.[1] Perhaps even more surprisingly, the most recent data from the large Royal College of General Practitioners' Oral Contraception Study, which started in 1968, showed a net benefit in long-term mortality overall for long-term users of the pill. This includes not only gynaecological benefits and protection from some cancers, but also decreased mortality from ischaemicheart disease among other conditions.[2]

Although 'the pill' is the most widely used and best known hormonal contraceptive, other methods have also gained widespread popularity. These include the combined hormonal vaginal ring, progestogen-only pill, etonogestrel implant, depot medroxyprogesterone acetate (DMPA) injection and levonorgestrel-containing intrauterine device (LNG-IUD).

This article identifies the noncontraceptive benefits of hormonal contraception, provides information on their mode of action, looks at the evidence for their use in clinical practice and puts these into perspective for the potential prescriber and user.

Development over the past 50 years

There have been considerable changes to the original 'birth control' pill, primarily in an effort to reduce the incidence of serious adverse effects, including thromboembolic events and side effects such as nausea. These changes have included decreasing the dose of ethinyloestradiol from 50 μg to 20 or 30 μg, and changing the dosing profile from the standard monophasic regimens to biphasic or triphasic regimens and then back again. More recent refinements to the pill include the reduction in the number of pill-free days from seven to four and the introduction of a new combined oral contraceptive (oestradiol and dienogest) that contains a natural oestrogen, and has dynamic dosing and only two days of placebo.

Different progestogens have been used in combination pills to improve acceptability without losing efficacy (see Table 1) and new delivery methods, such as vaginal rings, implants and hormonal-containing IUDs, have all been important in improving user friendliness by reducing the difficulties of daily compliance with oral delivery methods.

How do they work?

Suppression of ovulation is the critical mechanism of action of combined oestrogen- and progestogen-containing contraceptives. Progestogen alone also suppresses ovarian activity when given by injection or implant, but does not do so as reliably when ingested as a pill. Oral progestogen-containing contraceptives work primarily by producing a hostile cervical mucus at the opening of the cervix, thereby preventing the passage of sperm; however, all other forms of progestogen-containing contraceptives also have this capacity.

How do they provide therapeutic benefits?

Hormonal contraceptives have important therapeutic uses beyond contraception, as described below (Table 2).

Irregular bleeding

Combined hormonal contraceptives

Use of combined hormonal contraceptives will restore the regularity of cycles in women who have irregular bleeding due to oligo-ovulation or anovulation. Menstrual cycles can also be manipulated to the convenience of the user to miss withdrawal bleeding episodes altogether or to avoid menstrual-related symptoms, such as premenstrual-related headache. Studies have shown that it is safe to use combined hormonal contraceptives without placebo breaks for up to one year; however, many women prefer to do this for a shorter time as only about 50% achieve complete amenorrhoea after one year of continuous use.[3,4]

Menorrhagia, iron-deficiency anaemia and dysmenorrhoea

Levonorgestrel-containing intrauterine devices

The LNG-IUD is the nonsurgical treatment of choice for idiopathic menorrhagia. There is evidence for a mean reduction in blood loss of 97.7% and mean increase in haemoglobin levels of 17.2 g/L two years after insertion, thus also reducing the likelihood of menorrhagia-related iron deficiency anaemia.[5] The LNG-IUD has a therapeutic effect comparable with that of endometrial ablation up to two years after treatment. There have been no studies, however, comparing the LNG-IUD with ablation undertaken by the newer bipolar impedance-controlled technique.[6]

The LNG-IUD also performs well compared with a hysterectomy. In a trial of women who had been referred for specialist care of menorrhagia and randomly assigned to either a hysterectomy or the LNG-IUD, the IUD was found to be more cost effective and had no adverse effects on health-related quality of life or psychosocial well-being compared with a hysterectomy. Interestingly, this was still the case despite 42% of women assigned to the LNG-IUD eventually having a hysterectomy.[7]

Table 1. Hormonal contraceptives available in Australia

Contraceptive method	Component	Brand
Combined hormonal oral contraceptive pill	Ethinyloestradiol and levonorgestrel	Loette, Levlen ED, Logynon ED, Microgynon 20 ED, 30 ED and 50 ED, Microgynon 30, Microlevlen ED, Monofeme, Nordette, Trifeme, Triphasil, Triquilar ED
	Ethinyloestradiol and norethisterone	Brevinor 21 and 28, Brevinor-1 21 and 28, Improvil 28, Norimin 28, Norimin-1, Norimin-1 28, Norinyl-1 21 and 28, Synphasic 28
	Ethinyloestradiol and desogestrel	Marvelon 28
	Ethinyloestradiol and gestodene	Femoden ED, Minulet
	Ethinyloestradiol and cyproterone acetate	Brenda-35 ED, Diane-35 ED, Estelle-35 ED, Juliet-35 ED, Laila-35 ED
	Ethinyloestradiol and drospirenone	Yasmin, Yaz
	Ethinyloestradiol and dienogest	Valette
	Oestradiol valerate and dienogest	Qlaira
Combined hormonal vaginal ring	Ethinyloestradiol and etonogestrel	NuvaRing
Progestogen-only pill	Norethisterone	Micronor
	Levonorgestrel	Microlut
Progestogen implant	Etonogestrel	Implanon Implant
Progestogen intrauterine device	Levonorgestrel	Mirena
Progestogen injection	Depot medroxyprogesterone acetate	Depo Provera, Depo Ralovera

Combined hormonal contraceptives

Despite the absence of robust evidence of efficacy, the combined oral contraceptive pill is recommended as a first-line therapy for the treatment of idiopathic menorrhagia and dysmenorrhoea.[8,9] This recommendation is backed by observational studies and consensus opinion. The vaginal ring is assumed to act similarly and can also be recommended.

Etonogestrel implants and DMPA injections

Although the etonogestrel implant and DMPA injection are not licensed for the management of menorrhagia, the amenorrhoea that occurs in about 22% of implant users and 50% of DMPA users may be of therapeutic benefit. DMPA has traditionally been used to treat dysmenorrhoea but there is little formal evidence for this. In one study, dysmenorrhoea resolved in 77% of etonogestrel implant users who noted symptoms prior to initiation.[10]

Endometriosis and adenomyosis

As endometriosis is hormonally driven, contraceptives that suppress ovulation (i.e. the combined hormonal oral contraceptive, DMPA injection and etonogestrel implant) or reduce endometrial proliferation (i.e. the LNG-IUD) have been successfully used to treat symptoms of endometriosis.[11] There has been limited evidence of a histological effect, although one study showed a reduction in the stage of endometriosis after use of the LNG-IUD for six months.[12] There has been no benefit shown in using these contraceptive methods to improve fertility in women with endometriosis.

The LNG-IUD has also been shown to improve symptoms and reduce uterine volume in women diagnosed with adenomyosis.[13]

Ovarian cysts

The combined hormonal oral contraceptive pill has long been considered to reduce the risk of development of benign ovarian cysts, although the evidence is low grade and the clinical significance is doubtful. Indeed, no evidence supports its use in the treatment of ovarian cysts.[14]

Fibroids

The LNG-IUD reduces blood loss and pain in women with uterine fibroids, but does not appear to reduce the size of the fibroids, and there may be a higher risk of expulsion in such women. The presence of uterine fibroids is not, however, a contraindication to insertion of a LNG-IUD unless there is cavity distortion.[15] There are some data suggesting a protective effect of the combined hormonal oral contraceptive pill on the development of fibroids.[16]

continued

Table 2. Conditions that may be improved by hormonal contraceptives

System	Area affected	Condition	Method that assists	Method that may assist
Gynaecological	Menstrual cycle related	Menorrhagia or heavy menstrual bleeding,* dysmenorrhoea	Levonorgestrel IUD, combined hormonal contraceptives	DMPA injection, etonogestrel implant
		Irregular bleeding	Combined hormonal contraceptives	–
		Premenstrual syndrome	Combined hormonal contraceptives	–
	Ovarian cysts	Functional ovarian cysts, polycystic ovarian syndrome	Combined hormonal contraceptives	–
	Neoplasms	Ovarian cancer, endometrial cancer	Combined hormonal contraceptives	–
	Other conditions	Endometriosis, adenomyosis, fibroids	Levonorgestrel IUD, combined hormonal contraceptives	DMPA injection, etonogestrel implant
	Androgen-related	Acne, hirsutism	Combined hormonal contraceptives	–
Dermatological	Anaemia	Iron deficiency due to heavy menstrual bleeding	Levonorgestrel IUD, combined hormonal contraceptives, DMPA injection	Etonogestrel implant
Haematological	Menstrual cycle related	Epilepsy	–	DMPA injection
Neurological	Menstrual cycle related	Headache	Combined hormonal contraceptives	DMPA injection, etonogestrel implant
Endocrinological	Oestrogen deficiency	Premature ovarian failure, secondary amenorrhoiec states, perimenopause	Combined hormonal contraceptives	–

ABBREVIATIONS: DMPA = depot medroxyprogesterone acetate; IUD = intrauterine device.
* The term 'heavy menstrual bleeding' is being used more frequently to define the less clear 'menorrhagia' as defined by the International Federation of Gynecology and Obstetrics' working party on abnormal uterine bleeding. The more familiar term menorrhagia will be used in this article as the proposed new terminology has not yet been widely adopted.

Premenstrual syndrome

Premenstrual syndrome occurs in women of a reproductive age and appears to be related to ovulation. As an ovulation suppressor, the combined oral contraceptive pill could plausibly improve the symptoms of premenstrual syndrome. Unfortunately, studies with early levonorgestrel and norethisterone pills showed no beneficial effect, although anecdotally some women's symptoms appear to improve.[17]

More recently, specific attention has been focused on the progestogen drospirenone, which has both an antiandrogenic and an antimineralocorticoid effect. A 20 μg ethinyloestradiol and 3 mg drospirenone pill with 24 active pills and four placebos was shown in a study to be superior to placebo in the treatment of premenstrual dysphoric disorder over three months.[18] It is the only pill to have an indication for the treatment of premenstrual dysphoric disorder in women who have chosen oral contraceptives as their method of birth control. There are still, however, unanswered questions; the study mentioned above showed a large placebo effect and a Cochrane review concluded that it was unknown whether this formulation continued to work beyond three months, was helpful in women with less severe symptoms or was better than any other combined oral contraceptive.[19] It has also been postulated that the benefit may be due to the shorter duration of placebo.

Another study on drospirenone pills showed that a regimen of continuous active pills over 168 days led to a decrease in premenstrual symptoms compared with the traditional 21/7 pill-taking regimen.[20] Considering the limited treatment

Case study 1. A 39-year-old woman with heavy periods but no need for contraception

Initial presentation

Jane, aged 39 years, has no children. She is in a monogamous relationship with her partner who had a vasectomy six years ago. She had heavy periods before starting the combined oral contraceptive at the age of 20 years. She stopped the pill after her partner had a clear semen analysis, but since then she has had heavy periods. She often needs to wear a pad and a tampon together and not infrequently stains her underwear. There is no intramenstrual or postcoital bleeding. She has a 28-day cycle and has mild premenstrual symptoms.

Jane stopped smoking four years ago. She is normotensive and has a BMI of 28 kg/m^2. She is taking no medications.

Investigations

Full blood count showed a haemoglobin level of 113 g/L and a ferritin level of 10 µg/L. A vaginal ultrasound taken early in her cycle showed an endometrial thickness of 5 mm and no structural abnormalities.

Past management

Jane is reluctant to start taking the pill again because her 68-year-old mother was recently diagnosed with a deep venous thrombosis (DVT). Jane has tried both nonsteroidal anti-inflammatory agents and tranexamic acid with some effect.

Discussion

Jane would like to discuss treatment. She is not keen on any surgical intervention and would only consider endometrial ablation or a hysterectomy as a last resort. Progesterone in the form of norethisterone 5 mg three times daily from day 5 to 26 of her cycle is an option, as is danazol, but both have considerable side effects. A levonorgestrel-containing intrauterine device (LNG-IUD) would be an excellent choice as it greatly reduces menstrual bleeding and is rapidly reversible. Her nulliparity is not a contraindication, and in most circumstances the LNG-IUD can be inserted without a general anaesthetic.

The family history of a DVT in a first-degree relative aged over 45 years is not a contraindication to using combined oral contraceptives; however, Jane may feel less anxious taking a 'natural' oestrogen pill. These pills have a lower impact on proteins involved in coagulation; however, it is too early to say whether this results in a lower risk of DVT. A pill containing oestradiol valerate and dienogest has been recently made available in Australia. This pill has been shown to be very effective in the treatment of menorrhagia. DMPA injection is also an option for Jane because amenorrhoea occurs in around 50% of users.

options for women with premenstrual syndrome, the 20 µg ethinyloestradiol drospirenone pill is a useful therapeutic alternative.

Acne and hirsutism

The combined oral hormonal contraceptive pill has a beneficial effect on acne and hirsutism by decreasing bioavailable testosterone. This is largely achieved by the suppression of ovarian androgen production. In addition, the oestrogen-induced increase in sex-hormone binding globulin decreases the availability of free testosterone.

The choice of an oral contraceptive pill for women with acne is confusing. There are a number of pills with a specific indication for acne and it would be reasonable to conclude that these are the best choice. However, this indication is brand specific. For instance, there are two brands of the contraceptive pill containing 20 µg ethinyloestradiol and 100 µg levonorgestrel, one of which has an indication for acne and the other has not. As all pills decrease androgen availability they should all be effective. In fact, trials investigating any pill formulation have shown a beneficial effect on acne.

Another confusing area is the degree of androgenicity. Using levonorgestrel, the most androgenic progestogen, as a comparator, a feasible conclusion would be that pills containing a progestogen that is less androgenic (i.e. those containing norethisterone, gestodene or desogestrel) or that is antiandrogenic (i.e. those containing drospirenone, dienogest or cyproterone acetate) are the pills of choice for acne or hirsutism. However, strong evidence is lacking and a recent Cochrane review concluded that: 'few important differences were found between combined oral contraceptive types in their effectiveness for treating acne'.[21]

Although the etonogestrel implant has not been specifically trialed for its effect on acne (and in some women it is a side effect), 59% of women who had acne present when initiating implant use reported that their acne had improved or disappeared at the time of implant removal.[22]

Epilepsy related to menstrual cycling

In some women with epilepsy the variation of hormone levels throughout the cycle can lead to exacerbations of epileptic seizures.

The injectable progestogen DMPA is the best hormonal contraceptive for women with epilepsy who are taking enzyme-inducing antiepileptics (EIAEDs). This is because DMPA is not affected by enzyme induction as there is almost 100% clearance by the liver on first pass. This means that EIAEDs have no additional effect and blood levels are not affected. In

Case study 2. A young woman with a strong family history of ovarian and breast cancer

Initial presentation

Karen, aged 19 years, is in a six-month monogamous relationship with a male partner. She is currently using condoms but wants more reliable protection. Her mother was diagnosed with breast cancer at the age of 53 years. Her grandmother died of ovarian cancer aged 67 years and her only maternal aunt was diagnosed with ovarian cancer aged 44 years and is now in remission. None of her family members have had genetic testing. She is anxious about the effects of hormonal contraception on her risk of cancer, but would like to use the pill or the vaginal ring as she values highly cycle predictability.

Discussion

With such a strong family history of breast and ovarian cancer a referral to a specialist clinic to discuss Karen's risk is desirable, but it is not something she wants to consider now. There is a reasonable chance that her mother carries either a *BRCA1* or *BRCA2* mutation and, if so, there is a 50% chance Karen has inherited the mutation. The two issues to balance are the possible increased risk of breast cancer and the known decreased risk in ovarian cancer conferred by the pill.

Whether the pill increases the risk of breast cancer is controversial. If it does, the risk is considered to be small and there is no evidence of excess mortality from breast cancer in past or current pill users.[32] The UK Faculty of Reproductive and Sexual Healthcare Medical Eligibility Criteria for contraceptive use (available online at: www.ffprhc.org.uk/admin/uploads/UKMEC2009.pdf) do not rate a family history of breast cancer as a contraindication to use of the pill, but state that the risks outweigh the advantages for a woman with a known gene mutation that increases her risk of breast cancer. Mitigating this is a small study that showed that no excess risk of breast cancer was associated with pill use of more than five years in women who are *BRCA1* and *BRCA2* carriers.[33] Although the risks of breast cancer associated with the pill are uncertain, its use is known to decrease the risk of ovarian cancer in *BRCA1* and *BRCA2* carriers.

Outcome

At this stage Karen is not known to have a mutation that increases her risk of ovarian or breast cancer, but she is at moderately high risk. If she will not accept a progestogen-only method of contraception, the pill could be considered after careful discussion of the advantages in relation to ovarian cancer and the possible disadvantages related to breast cancer.

addition, DMPA injections may add to epileptic control for some women because of their effect on ovulation suppression and the resulting lack of variation in hormone levels with the menstrual cycle.[23]

Hypogonadism

In women who are deficient in oestrogen, most commonly seen as secondary amenorrhoea (premature ovarian failure that is either spontaneous or induced as a by-product of surgery, chemotherapy or radiotherapy), the use of combined hormonal methods (oral pill or vaginal ring) is an important aspect of management. These women frequently experience significant vasomotor symptoms. Combined hormonal contraceptives manage these symptoms by acting as a form of hormone replacement. They are particularly useful in perimenopausal women, who have no contraindications to the use of oestrogen-containing contraceptives, because of their superior cycle control compared with standard hormone replacement therapy. Bone density may also be maintained in the later reproductive years in women who use the combined contraceptive pill for more than 10 years.[14]

Ovarian cancer

Over the past 30 years, overwhelming evidence has emerged that the combined hormonal oral contraceptive pill reduces the incidence of ovarian cancer. An overview of 45 studies published in 2008, postulated that some 200,000 cases of ovarian cancer and 100,000 deaths have been prevented since the introduction of the pill 50 years ago.[1] Indeed, there have been calls for it to be made available 'over the counter' in the UK because of this important benefit. Significantly, this advantage lasts for up to 30 years and appears to carry through to women who have a risk of inherited ovarian cancer (those who are carriers of the *BRCA1* or *BRCA2* mutations)[1,24] (see case study 1 in the box on page 54).

Endometrial cancer

Similarly, endometrial cancer has also shown a significant and compelling decline in prevalence and mortality since the introduction of the oral contraceptive pill. The Royal College of General Practitioners' (UK) Oral Contraceptive Study found a 42% reduced risk of endometrial cancer in ever users of oral contraceptives compared with never users. The reduction in risk was greater with prolonged use of the oral contraceptive pill and protection lasted for more than 15 years.[25] Therefore, in practice, if a woman stops taking the combined hormonal oral contraceptive pill at 45 years of age, she has protection until the age of 60 years.

continued

Is this huge reduction in gynaecological cancer plausible?

Ovarian cancer

If ovulation is prevented, there is less injury and subsequent repair of the epithelium of the ovary, as well as decreased direct pituitary hormone effects on the ovarian epithelium. 'Incessant ovulation' is a relatively new phenomenon in evolutionary terms. For the first time in history, women can regulate their fertility by preventing a pregnancy every one to two years. The risk of ovarian cancer appears to be decreased by the number of live births, incomplete pregnancies and the use of the combined oral contraceptive.[26]

Endometrial cancer

With the suppression of ovulation caused by the combined hormonal oral contraceptive, endogenous follicular oestrogen secretion production is markedly suppressed. Also, as combined hormonal contraception is by definition an oestrogen accompanied by a progestogen, there is no time when oestrogenic target tissues are stimulated by oestrogens without a progestogen component.

The progestogenic effect is antioestrogenic, causing:

- a decrease in the synthesis of oestrogen receptors
- a stimulation of the enzyme oestradiol 17β-dehydrogenase within endometrial cells (this enzyme converts oestradiol to oestrone, which is a far weaker oestrogen), thus decreasing oestrogenic activity.

These effects tend to decrease the proliferation of the glandular epithelium and the thickness of the endometrium, reducing the potential for endometrial hyperplasia and progression to cancer.

Are there any proven risks?

Combined hormonal pill

Current users of the combined pill have a small increase in the risk of ischaemic heart disease and stroke. These risks increase with age and are highest in women who smoke cigarettes, who take hypertensive medication or with long-term diabetes.[27] The risk of venous thromboembolism (VTE) is also more than doubled and progestogen-only methods are indicated if the woman has a past history of VTE or a family history suggestive of a genetic predisposition.[28] Cancer of the cervix is also increased;[29] however, this risk to the user is small, most likely due to Australia's excellent cervical screening program. Although the risk of hepatic cancer is increased,[30] it is a rare condition in women of a reproductive age and use of the pill does not further increase its risk in women with chronic hepatitis.[31]

Whether the pill increases the risk of breast cancer remains controversial. Its use is not contraindicated in women with a family history of breast cancer. However, it is relatively strongly contraindicated in women with a known gene mutation that increases their risk of breast cancer, despite studies having not conclusively shown an additional risk in these women from its use (see case study 2 in the box on page 56).[32-34]

Progestogen-only methods

There is a known reduction in bone density in DMPA users, which is thought to be slowly regained after cessation.[35] Limited evidence on other serious risks is reassuring.

Conclusion

Hormonal contraceptives have important therapeutic uses beyond contraception. They have made the management of bleeding problems significantly safer by reducing the reliance on surgical alternatives such as a hysterectomy. They have also improved the self-esteem of many women who suffer from androgen-related conditions, such as acne and hirsutism and, most significantly, are thought to reduce mortality from ovarian and endometrial cancers. Unfortunately, many women, media commentators and even doctors appear to be afraid of hormonal contraceptive methods.

The important take-home message is that hormonal contraceptives, used appropriately and with regard to medical eligibility based guidelines, such as those published by the World Health Organization (www.who.int/reproductivehealth/publications/family_planning/9789241563888/en/index.html), provide safe, effective contraception and protection against ovarian and endometrial cancers and assist in the management of specific medical conditions. MT

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A list of references is available on request to the editorial office.

COMPETING INTERESTS: Dr Read is an independent consultant and has provided expert opinion to pharmaceutical companies including Bayer Schering Pharma, MSD and Pfizer. She has received support to attend conferences from Bayer Schering Pharma and is a principal investigator for a MSD funded contraceptive trial. Dr McNamee has provided expert opinion for Bayer and Schering Plough as part of her employment with Family Planning Victoria. She has received support for conference attendance from Organon (now MSD).

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