NPTC Drug Class Review: Oral Contraceptives

Introduction

The purpose of this review is to support the IHS National P&T Committee in making recommendations for the IHS National Core Formulary (NCF) regarding the clinical effectiveness (overall clinical utility) of the available oral contraceptive agents. This review does not include injectable, transdermal, vaginal ring contraceptives, implants, devices (female condoms, diaphragms), IUDs, or over-the-counter products. The agents included are outlined in Table 1.

For formulary purposes, the contraceptives are divided into the following categories, based on regimen, dosage form, and estrogen content (see Table 1). These categories do not take into account all differences among agents (e.g., progestogen content), but do serve to reduce the large number of available agents into manageable categories.

Table 1: Contraceptive Categories

Type of Contraceptives	Products
Monophasic OCs with 20 mcg EE	20 mcg EE/1 mg norethindrone acetate 20 mcg EE/0.09 mg levonorgestrel 20 mcg EE/0.1 mg levonorgestrel 20 mcg EE/3 mg drospirenone
Monophasic OCs with 30 mcg EE	30 mcg EE/0.3 mg norgestrel 30 mcg EE/0.5 mg norgestrel 30 mcg EE/1 mg norethindrone 30 mcg EE/1.5 mg norethindrone acetate 30 mcg EE/0.15 mg levonorgestrel (+ 10 mcg EE) 30 mcg EE/3 mg drospirenone
Monophasic OCs with 35 mcg EE	35 mcg EE/0.4 mg norethindrone 35 mcg EE/0.5 mg norethindrone 35 mcg EE/1 mg norethindrone 35 mcg EE/1 mg ethynodiol diacetate 35 mcg EE/0.25 mg norgestimate
Monophasic OCs with 50 mcg EE or mestranol	50 mcg mestranol/1 mg norethindrone 50 mcg EE/1 mg norethindrone 50 mcg EE/1 mg ethynodiol diacetate
Biphasic OCs	35 mcg EE/0.5/1 mg norethindrone 20/10 mcg EE/0.15/0 mg desogestrel
Triphasic OCs	25 mcg EE/0.18/0.215/0.25 mg norgestimate 30/40/30 mcg EE/0.05/0.075/0.125 mg levonorgestrel 35 mcg EE/0.18/0.215/0.25 mg norgestimate 35 mcg EE/0.5/1/0.5 mg norethindrone 35 mcg EE/0.5/0.75/1 mg norethindrone 20/30/35 mcg EE/1 mg norethindrone 25 mcg EE/0.1/0.125/0.15 mg desogestrel
Quadriphasic OCs	3/2/2/1 mg estradiol valerate/2/1 mg dienogest
Progestogen-only OCs	0.35 mg norethindrone 0.075 mg norgestrel
Emergency contraception	0.75 mg levonorgestrel

Oral contraceptives are typically taken in a 21-day on, 7-day off regimen. However, Yaz (drospirenone/EE) and Loestrin Fe 24 (norethindrone/EE) are given as 24 days of hormone treatment, followed by 4 days of placebo, and Natazia (estradiol valerate/dienogest) is given for 26 days of hormone treatment, followed by 2 days of placebo. There are four extended cycle products: Seasonale, Jolessa, Quasense, and Seasonique (levonorgestrel/EE) . The first three products are taken on a 91-day cycle with 84-days of active pills followed by 7 days of placebo. Seasonique is taken on a 91-day cycle , but instead of placebo, the patient takes 7 days of 10 mcg EE. Lybrel (levonorgestrel/EE) is taken continusously with no placebo.

Table 2: Super Mega Contraceptive Table

	Brand Name	Manufacturer	Estrogen (mcg)	Progestogen	Progestogen Activity	Estrogen Activity	Androgen Activity
Monophasic OCPs with 20mcg EE	Alesse	Wyeth	EE 20	0.1 mg levonorgestrel	Low	None	High
	Aviane	Duramed					
	Lutera	Watson					
	Lessina	Barr					
	Levlite	Berlex					
	Sronyx	Watson					
	Lybrel	Wyeth					
	Junel 1/20	Barr	EE 20	1.0 mg norethindrone acetate	Low	Low	Low
	Loestrin 1/20	Warner Chilcott					
	Microgestin 1/20	Watson					
	Junel Fe 1/20	Barr					
	Loestrin Fe 1/20*	Warner Chilcott					
	Microgestin Fe 1/20	Watson					
	Loestrin 24 Fe	Warner Chilcott	EE 20	1.0 mg norethindrone acetate	Low	Low	Low
	Yaz	Berlex	EE 20	3 mg drospirenone	No data	Low	None
Monophasic OCPs with 30mcg EE	Levlen 28	Berlex	EE 30	0.15 mg levonorgestrel	Low	None	High
	Levora 0.15/30-28	Watson					
	Nordette-28	Duramed					
	Portia-28	Barr					
	Seasonale	Duramed					
	Quasense	Watson					
	Jolessa	Barr					
	Seasonique	Duramed	EE 30+ 10				
	Cryselle	Barr	EE 30	0.3 mg norgestrel	Intermed	None	Intermed
	Lo/Ovral	Wyeth					
	Low-Ogestrel	Watson					
	Apri	Barr	EE 30	0.15 mg desogestrel	High	None	Intermed
	Desogen	Organon					
	Ortho-Cept	Ortho					
	Reclipsen	Watson					
	Solia	Prasco					
	Junel 1.5/30	Barr	EE 30	1.5 mg norethindrone acetate	Low	Low	Low
	Loestrin 1.5/30	Duramed					
	Microgestin 1.5/30	Watson					
	Junel Fe 1.5/30	Barr					
	Loestrin-FE 1.5/30	Duramed/Barr					
	Microgestin Fe 1.5/30	Watson					
	Yasmin	Berlex	EE 30	3 mg drospirenone	No data	Low	None

	Brand Name	Manufacturer	Estrogen (mcg)	Progestogen	Progestogen Activity	Estrogen Activity	Androgen Activity
Monophasic OCPs with 35mcg EE	Brevicon	Watson	EE 35	0.5 mg norethindrone	Low	Low	Low
	Modicon	Ortho					
	Necon	Watson					
	Nortrel 0.5/35	Barr					
	Ovcon-35	Warner-Chilcott	EE 35	0.4 mg norethindrone	Low	Low	Low
	Femcon Fe (chewable)						
	Balziva	Barr					
	Mononessa	Watson	EE 35	0.25 mg norgestimate	Low	No	Low
	Ortho-Cyclen	Ortho					
	Previfem	Teva					
	Sprintec	Barr					
	Necon	Watson	EE 35	1.0 mg norethindrone	Low	Low	Low
	Norinyl 1+35	Watson					
	Nortrel	Barr					
	Ortho-Novum 1/35	Ortho					
	Demulen 1/35	Pharmacia/Upjohn	EE 35	1.0 mg ethynodiol diacetate	Low	Intermed	Low
	Kelnor	Barr					
	Zovia 1/35E	Watson					
Monophasic OCPs with 50mcg EE or mestranol	Necon	Watson	Mes 50	1 mg norethindrone	Low	Low	Low
	Norinyl 1+50	Watson					
	Ortho-Novum 1/50	Ortho					
	Ovcon-50	Warner Chilcott	EE 50	1 mg norethindrone	Low	Low	Low
	Demulen 1/50	Pharmacia/Upjohn	EE 50	1 mg ethynodiol diacetate	Low	Intermed	Low
	Zovia 1/50E	Watson					
	Ogestrel	Watson	EE 50	0.5 mg norgestrel	Intermed	None	Intermed
	Ovral-28	Wyeth					
Biphasic OCPs	Necon	Watson	EE 35	0.5 mg/1.0 mg norethindrone	Low	Low	Low
	Ortho-Novum 10/11	Ortho					
	Kariva	Barr	EE 20/0.01mg	0.15/0 mg desogestrel	High	None	Intermed
	Mircette	Duramed/Barr					

	Brand Name	Manufacturer	Estrogen (mcg)	Progestogen	Progestogen Activity	Estrogen Activity	Androgen Activity
Triphasic OCPs	Ortho Tri-Cyclen Lo	Ortho	EE 25	0.18/0.215/0.25 mg norgestimate	Low	None	Low
	Ortho Tri-Cyclen	Ortho	EE 35	0.18/0.215/0.25 mg norgestimate	Low	None	Low
	Trinessa	Watson					
	Tri-Previfem	Teva					
	Tri-Sprintec	Barr					
	Enpresse	Barr	EE 30/40/30	0.05/0.075/0.125 mg levonorgestrel	High	None	High
	Tri-levlen	Berlex					
	Triphasil	Wyeth					
	Trivora	Watson					
	Aranelle	Barr	EE 35	0.5/1/0.5 mg norethindrone	Low	Low	Low
	Leena	Watson					
	Tri-Norinyl	Watson					
	Necon 7/7/7	Watson	EE 35	0.5/0.75/1 mg norethindrone	Low	Low	Low
	Nortrel 7/7/7	Barr					
	Ortho-Novum 7/7/7	Ortho					
	Cesia	Prasco	EE 25	0.1/0.125/0.15 mg desogestrel	High	None	Intermed
	Cyclessa	Organon					
	Velivet	Barr					
	Estrostep Fe	Warner-Chilcott	EE 20/30/35	1.0 mg norethindrone	Low	Low	Low
	Tri-Legest FE	Barr					
	Tilia FE	Watson					
Quadriphasic OCPs	Natazia	Bayer	Estadiol valerate 3/2/2/1 mg	2/1 mg dienogest			Low
Progestogen-Only OCPs	Errin	Barr	-	0.35 mg norethindrone	Low	Low	Low
	Ortho Micronor	Ortho					
	Jolivette	Watson					
	Camila	Barr					
	Nora-BE	Watson					
	Nor-QD	Watson					
	Ovrette	Wyeth	-	0.075 mg norgestrel	Intermed	None	Intermed
Emergency Contraceptives	Plan B	Duramed	-	0.75 mg levonorgestrel			
	Next Choice	Watson	-	0.75 mg levonorgestrel			

FDA-Approved Indications and Off-Label Uses

All contraceptives are FDA-approved for the prevention of pregnancy. Relatively few contraceptive products have additional FDA indications (acne: Ortho Tri-Cyclen, Estrostep Fe), although most if not all have non-contraceptive benefits. Historically, Ortho Tri-Cyclen's approval for acne has given it an enormous marketing advantage.

Non-contraceptive benefits of oral contraceptives include reduction of acne, dysmenorrhea, premenstrual dysphoric disorder (PMDD), endometriosis pain, and menstrual migraines.

Currently, the only contraceptive product approved and marketed for emergency conception is a progestogen-only product, levonorgestrel 0.75 mg (Plan B), although many oral contraceptives can be used for this purpose.

Coverage Issues / Methods

- While there are a large number of OCs and other options (e.g., patch, ring, injectable), they are based on relatively few active ingredients. The differences (of varying clinical significance) lie in strength of the estrogen and progestogen components, differences in progestogen characteristics, regimens, and dosage forms. Wide intra- and inter-patient variability exists.
- Differences in efficacy for the prevention of pregnancy do not loom large in this class. Specific products may offer slightly decreased efficacy (progestogen-only OCs and possibly low estrogen products), but in general all of the contraceptive options included in this review are highly effective at preventing pregnancy when used correctly. Differences in efficacy for non-contraceptive considerations (such as acne, menstrual migraines, endometriosis pain, premenstrual syndrome or premenstrual dysphoric disorder) may be reasonably anticipated based on differences in estrogen or progestogen content. Products also differ with respect to cycle control issues (e.g., breakthrough bleeding and spotting), adverse effects (e.g., bloating, weight gain, androgenic effects), or safety (e.g., thromboembolic events).
- Comparative trials in this area are primarily focused on comparing newly introduced products to established products. These trials are probably not sufficient to draw systematic conclusions; the focus in this review is primarily on the attempts of systematic reviews (largely Cochrane reviews) to do so, not on results of individual trials. Accordingly, the authors first searched Medline and other online sources for applicable systematic reviews, meta-analyses, and review articles. In addition, contraceptive chapters from various standard medical texts were consulted for background information. Guidelines from the World Health Organization were also consulted, although these were of limited usefulness to this review as they primarily focus on the proper selection of contraceptive options at a more general level (e.g., use of IUDs vs. barrier methods vs. OCs). The review did not include trials or other information concerning products not available in the U.S. Product information was obtained from manufacturers only when considered necessary, especially for newly approved products.

Pharmacology, Dosing, and Administration

Combined OCs

Combined estrogen/progestogen contraceptives provide contraception by several mechanisms of action, including inhibition of the midcycle surge of gonadotropin secretion, which prevents ovulation; suppression of gonadotropin secretion during the follicular phase of the menstrual cycle, which prevents follicular maturation; thickening of cervical mucus, which blocks sperm penetration and entry into the upper reproductive tract; thinning of endometrium, which may inhibit implantation; and slowing of tubal and endometrial motility.

Estrogen content in combined OCs has progressively decreased in response to epidemiological studies linking combined OC use to breast cancer and major adverse events, including cerebrovascular events, thromboembolic events, and myocardial infarction. There is little variation in estrogen content other than strength (all combined OCs contain EE or mestranol, a prodrug of EE). The highest EE content currently available in an OC in the U.S. is 50 mcg. Low estrogen (20-30 mcg EE) combined OCs are most commonly used.

In contrast to estrogens, a number of different progestogens are used in contraceptive products. By definition, progestogens bind to and activate progesterone receptors, but may also bind to other receptors. Based on chemical structure, there are three basic groups:

- pregnanes (medroxyprogesterone acetate),
- estranes (norethindrone and its derivatives, such as ethynodiol diacetate), and
- gonanes (levonorgestrel, norgestimate, desogestrel, and gestodene)

Drospirenone is a derivative of spironolactone with antimineralocorticoid and antiandrogenic properties similar to progesterone. In addition to progesterone receptors, drospirenone binds to aldosterone receptors in the kidney; the effect is similar to 25 mg of spironolactone.

Progestogen-only vs. combined OCs

Progestogen-only OCs (also called the "minipill") do not consistently inhibit ovulation (about 40% of cycles result in ovulation). The efficacy of progestogen-only OCs depends largely on changes in mucosal viscosity and other changes that produce an inhospitable uterine environment. Drawbacks compared to combined OCs include more breakthrough bleeding and slightly higher failure rates, as well as the need for more exact use—they must be taken daily, without a pill-free interval, at approximately the same time per day. Variation of only a few hours can reduce contraceptive effectiveness; a back-up method of contraception is needed if a pill is missed or if there is more than a three-hour delay in dosing.

Progestogen-only OCs are an option for women who need to avoid estrogen. Women ≥ 40 may also be candidates, due to the increased risk of thromboembolic adverse events and the naturally reduced risk of pregnancy in this age group. Progestogen-only OCs may also be an option for women who are breast-feeding, although this point has been disputed. The premise is that the amount of progestogen excreted into milk is low and does not affect quality and composition of the milk, and a minor potential decrease in contraceptive effectiveness can be tolerated since lactation provides additional protection against conception (see the safety section).

1st vs. 2nd vs. 3rd generation products

Oral contraceptives are sometimes divided into generations, based on both estrogen and progestogen content. First generation products are considered to be those with ≥ 50 mcg of estrogen. Second generation products contain < 50 mcg estrogen and one of the following progestogens: norethindrone, ethynodiol diacetate, levonorgestrel, or norgestrel. Third generation products contain one of the following progestogens, which are less androgenic than 2nd generation products: desogestrel, norgestimate, or gestodene (not marketed in the U.S.). Products with the progestogen drospirenone are still usually referred to as unclassified.

A recent Cochrane review[1] used generational terminology a little differently, to refer to progestogen content only. First-generation progestogens were considered to be norethindrone and ethynodiol diacetate, second-generation products levonorgestrel and norgestrel, and third-generation products desogestrel, norgestimate, and gestodene. Drospirenone was considered unclassified. References to generations of contraceptives in this review refer to this classification method.

The issue of whether third-generation products are associated with an increased thromboembolic risk compared to second-generation products has been controversial (see safety section). Second and third generation products appear to offer some advantages over first generation products with respect to cycle control (see efficacy section).

Monophasic vs. biphasic vs. triphasic combined OCs

Biphasic and triphasic oral contraceptives attempt to "mimic" changes in levels of estrogen and progesterone seen during the normal menstrual cycle, in an attempt to decrease adverse effects by decreasing the total load of contraceptive steroids.[2] This was probably primarily a reaction to the controversy about increased thromboembolic events with 3rd vs. 2nd generation progestogens, since lower total amounts of progestogens can be achieved by providing a varying amount through the cycle.

In one type of biphasic OC, the EE dose is constant throughout the 21-day cycle, but the progestogen dose increases at mid-cycle (day 11 on) (e.g., Ortho Novum 10/11). These products represent the biphasic products initially introduced to the market. Triphasic OCs, which vary daily doses of estrogen and/or progestogen three times during the treatment period, rapidly became more popular than biphasic OCs, due to a suggested increase in breakthrough bleeding with the biphasics.[3] Of the available triphasic products, five vary the amount of progestogen, one varies the amount of estrogen, and one varies both (see Table 1).

Although classified as a biphasic product, Mircette and its equivalents may be more similar to a monophasic product with supplemental estrogen given during the off-cycle (21 days of EE 20 mcg/desogestrel 150 mcg followed by 2 days of placebo and 5 days of 10 mcg EE). This regimen may be useful in perimenopausal women, due to the more constant estrogen formulation.

Alternative regimens (extended use, continuous use, 24-day cycle)

Combined OCs are commonly administered on a 28-day cycle: 21 days of active medication followed by 7 days medication-free. Most of the commonly used products provide 7 placebo tablets to be taken (or discarded) during the medication-free period in order to improve compliance. Five products are specifically approved and packaged for extended use. Seasonale, Quasense, and Jolessa are taken on a 91-day cycle with 84-days of active pills followed by 7 days of placebo. Seasonique is taken on a 91-day cycle, but instead of placebo, the patient takes 7 days of 10 mcg EE. Lybrel (levonorgestrel/EE) is taken continuously with no placebo. Two products offer a 24-day on, 4-day off cycle (Yaz, Loestrin 24 Fe). One product offers a quadriphasic cycle with 22 days of estradiol valarate/dienogest, 4 days of estradiol valerate alone, and 2 days off (Natazia).

Emergency (post-coital) contraception

The only product currently labeled as emergency contraception is levonorgestrel 0.75 mg (Plan B). A combination emergency contraception product (Preven) was discontinued in 2004. However, many oral contraceptives can be used as emergency contraception, both progestogen-only OCs and combined OCs (based on the Yuzpe regimen). The FDA has declared the following brands to be safe and effective for emergency contraception (one dose within 72 hours after unprotected intercourse and a second dose 12 hours later): Ovral (1 dose = 2 white pills), Alesse (1 dose = 5 pink pills), Nordette or Levlen (1 dose = 2 light-orange pills), Lo/Ovral (1 dose = 4 white pills), Triphasil or Tri-Levlen (1 dose = 4 yellow pills). Progestogen-only regimens such as Plan B have been shown to be more effective and better tolerated than combination OCs.

Plan B prevents pregnancy primarily by suppressing the mid-cycle surge of leutinizing hormone (LH), preventing follicular maturation and ovulation. Depending on timing, Plan B may also block the implantation of a fertilized egg due to thickening of cervical mucus. Therefore, individuals who believe that life begins at conception may have an ethical/moral objection to prescribing or dispensing Plan B. Plan B is not effective once implantation has occurred and will not disrupt an established pregnancy.

Pharmacokinetics

Estrogens - Almost all currently marketed combination OCs contain ethinyl estradiol (EE) as the estrogen component. Mestranol, a prodrug that must be converted to EE to become biologically active, is included in a few older products. The pharmacokinetics and metabolism of mestranol are similar to EE, except for a longer time to maximum concentration (Tmax).

EE is rapidly absorbed from the gastrointestinal tract, but undergoes enterohepatic circulation. Ethinyl estradiol sulfates can be hydrolyzed by intestinal bacteria, with some of the deconjugated estrogen reabsorbed. There appears to be considerable intra- and inter-patient variability in the amount of EE absorbed, circulating EE concentrations, and elimination time.

Progestogens – Orally active progestogens are rapidly absorbed and transported to the liver through the portal circulation, where they may undergo first-pass liver metabolism before entering the general circulation. First-pass metabolism may include glucuronidation and sulfuration, which facilitate excretion by the kidney. In the general circulation, progestogens are present either in the free form or bound to albumins or sex hormone-binding globulin (SHBG).

Drospirenone is a derivative of spironolactone with anti-mineralocorticoid and anti-androgenic properties similar to progesterone. In addition to progesterone receptors, drospirenone binds to aldosterone receptors in the kidney; the effect is similar to 25 mg of spironolactone. It is metabolized only to a minor extent, primarily by CYP 3A4 and has no active metabolites. It has a 30-hour half-life. It does not bind to SHBG.

Efficacy/Effectiveness

Contraceptive Effectiveness

The effectiveness of contraception is typically expressed as both the theoretical effectiveness (pregnancy rate given correct use on every occasion) and actual effectiveness (typically lower due to inconsistent or incorrect use). The Pearl Index (the number of unintended pregnancies per 100 women per year) is often used to quantify effectiveness. OCs are associated with a very low pregnancy rate if taken correctly, but actual pregnancy rates are substantially higher.

Table 3 – Percent of women experiencing an unintended pregnancy within the first year of typical or perfect use*

Method	% of women with unintended pregnancy within 1st year of use		Percent of Women Continuing Use at 1 Year
	Typical Use	Perfect Use	
No method	85	85	
Spermicides	29	15	
Withdrawal	27	4	43
Periodic abstinence	25	1-9*	51
Cervical cap with spermicide			
Parous women	32	26	46
Nulliparous women	16	9	57
Diaphragm with spermicide	16	6	57
Condom			
Reality female condom	21	5	49
Male condom	15	2	53
Combined and progestogen-only OCs	8	0.3	68
Ortho-Evra patch	8	0.3	68
Nuvaring	8	0.3	68
DMPA injections (every 3 mo)	3	0.3	56
IUD	0.1-0.8**	0.1-0.6**	78-81
Implant (Implanon)	0.38		
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

* chart adapted from Trussell (2004)[4] by Hatcher (2004)[5]; results for the patch and vaginal ring are presumably set equal to OCs; ** depending on method; *** depending on type of IUD, Copper T (Paragard) or levonorgestrel-releasing (Mirena)

By and large, the efficacy of various oral contraceptives in preventing pregnancy appears to be similar. An exception may be the progestogen-only products, which require more careful adherence. There is some concern that contraceptive effectiveness may be compromised with the lowest dose estrogen products.

Emergency contraception – Plan B has an efficacy rate of about 95% if taken within 24 hours of unprotected intercourse, 86% within 25-48 hours, and 58% within 49 to 72 hours.[6] Since obtaining a prescription and locating a pharmacy may take time, women may not be able to start taking Plan B within the most effective time period. Proposed solutions have included collaborative agreements allowing

pharmacists to dispense Plan B without a direct order from a physician, provision of advanced supplies, and over-the counter status.[7-10]

Cycle Control

In some cases, contraceptives are prescribed primarily to provide cycle control (e.g., reducing heavy menstrual bleeding, menstrual pain, and regulating irregular cycles). Extended cycle treatment may be aimed at producing minimal or no bleeding for three months or longer. In this regard, cycle control may be regarded as an efficacy issue. On the other hand, cycle control issues such as spotting, breakthrough bleeding, and early withdrawal bleeding represent overall undesirable adverse effects that may distress patients and affect compliance with therapy. Trials that assess cycle control also frequently assess the incidence of other adverse effects. For the sake of efficiency, all of these results will be discussed in this section.

Cycle problems tend to lessen within a few months of OC initiation, regardless of formulation. Strategies for dealing with cycle problems include: education regarding the decrease in problems during the first 3 months of use and an attempt not to make a change in formulation during this period; consideration of factors that can contribute to problems, such as missed doses, chlamydial infections, smoking, and interacting medications; changes in regimen (adding estrogen or decreasing progestogen if bleeding occurs early in the cycle, adding progestogen if it occurs late in the cycle, or doubling active pills until the bleeding stops or for the rest of the cycles); or providing a course of non-steroidal anti-inflammatory drugs.[11]

It is worth noting that studies of cycle control tend to have methodological problems, including small sample size, lack of control for other factors that may affect the incidence of bleeding (e.g., chlamydial infection, age, smoking, missed pills, interacting medications), differences in study design/analysis, and differences in definitions of bleeding and spotting.[11]

Because of the lack of uniformity in studies of cycle control, the World Health Organization has issued recommendations aimed at standardizing collection and analysis of data, including definitions of "bleeding" (requires sanitary protection) and "spotting" (does not require protection) and a "bleeding/spotting" episode (one or more days with bleeding or spotting bounded by days without bleeding or spotting). The WHO advises that the woman rather than the cycle should be used as the unit of analysis (to avoid placing excessive weigh on results from women who contribute more cycles of data) and that outcomes should be measured using a reference period of at least 84-90 days (to identify changes over time while still fairly assessing bleeding patterns). Terms used to assess bleeding during the pill-free period should be defined, and at least five bleeding outcomes should be included: proportion of women with prolonged, frequent, infrequent, or irregular bleeding/spotting episodes and those with amenorrhea during the reference period.[12]

Estrogen content & cycle control

As the estrogen content of OCs has declined, higher breakthrough bleeding and spotting rates have been noted, along with a possible decrease in contraceptive efficacy.[13] Low estrogen OCs may be more influenced by missed doses or drug interactions, [14] and may not provide the same non-contraceptive benefits as higher estrogen products, such as reduction in risk of ovarian cancer, protection against functional ovarian cysts, and improvements in acne.[13] This should be balanced against a lower risk of thromboembolic events and a decrease in estrogen-related adverse effects. Determination of the "best" estrogen dose—reliable pregnancy prevention with acceptable cycle control and minimal adverse effects—is complicated by wide inter-patient variability in hormonal blood levels.

Gallo et al (2005)[13] performed a systematic review of trials comparing a combined OC containing ≤ 20 mcg EE with a combined OC containing > 20 mcg EE for at least three treatment cycles. Outcome measures included contraceptive effectiveness, discontinuation due to bleeding-related reasons or other adverse effects, bleeding patterns (based on WHO recommendations for reporting cycle control results), and adverse effects. Reviewers did not attempt to quantify thromboembolic risk, since these events are too rare for differences to be detectable in randomized controlled trials. Eighteen trials (17 different pairs of combined OCs) were included out of a total of 69 English-language reports identified. Methodological problems included lack of details concerning blinding (12 trials were open-

label or did not mention blinding), methods of randomization, number of participants screened, and analytical methods (e.g., intent-to-treat).

Reviewers noted that while no differences were reported between groups in the 11 combined OC pairs for which contraceptive effectiveness was reported, this does not provide sufficient evidence to conclude that combined OCs with 20 mcg EE are equal to higher-estrogen products in preventing pregnancy. Most studies were underpowered (pregnancy is a rare outcome), studies could not be combined for meta-analysis due to difference in progestogen content, and effects on contraceptive effectiveness arising from an reduced margin of safety from missed doses were probably compensated for by trial exclusions of women for protocol violations, including failure to adhere to daily dosing requirements.

Discontinuation rates did not vary substantially, although four comparisons showed higher discontinuation rates for women receiving combined OCs with 20 mcg EE and there were more discontinuations (overall, due to medical reasons, and due to amenorrhea) with EE 20 mcg/norethindrone 1 mg vs. 5 higher-estrogen comparators. Methodological problems include lack of information concerning discontinuations due to specific adverse effects (e.g., amenorrhea vs. irregular bleeding) – an objection tied to study size, since most trials were too small to detect such differences.

In a number of cases, combined OCs with 20 mcg EE were associated with higher rates of lack of bleeding (amenorrhea and infrequent bleeding) and changes in bleeding (irregular, prolonged, frequent, and breakthrough bleeding) compared to ≥ 20 mcg EE. Methodological issues include differences in how outcomes are defined in various studies as well as the fact that differences in progestogen content may affect cycle control.

Three of six combined OC pairs with data for adverse effects (proportion of women experiencing an outcome) reported differences between lower- and higher-estrogen products. In one study, rates of headache, mood changes, and nausea / diarrhea / vomiting were higher for EE 20 mcg/desogestrel 150 mcg than EE 30 mcg/desogestrel 150 mcg. On the other hand, two studies (one comparing EE 20 mcg/desogestrel 150 mcg to EE 30-40-40 mcg / gestodene 50-70-100 and the other comparing EE 20 mcg/levonorgestrel 100 mcg to EE 35 mcg / norethindrone 500-750-1000 mcg) reported lower rates of breast pain in the lower-estrogen group. The first of these two studies also reported lower rates of dizziness and nausea in the lower-estrogen group. Overall, reviewers did not draw conclusions concerning differences in potential for adverse effects.

Progestogen content & cycle control

Progestogen content may also affect cycle control. In a Cochrane review last updated in 2005,[1] Maitra et al evaluated randomized trials evaluating combined OCs with < 50 mcg EE comparing 1) a third-generation progestogen (desogestrel, norgestimate, gestodene) to a second-generation (levonorgestrel, norgestrel), 2) a third-generation progestogen to a first-generation (norethindrone, ethynodiol), 3) a second-generation to a first-generation, or 4) comparisons between products containing a certain progestogen. The minimum duration was six cycles. Trials involving monophasic and multiphasic products were analyzed separately.

Outcome measures included contraceptive effectiveness, discontinuation rates, cycle control, adverse effects, and women's satisfaction with the method of contraception. Twenty-two trials were included in the review, 16 comparing monophasic OCs and six comparing triphasic OCs. Two trials contained drospirenone; all others contained first-, second-, or third-generation progestogens.

- *3rd vs. 2nd generation progestogens* – two trials compared monophasic gestodene with monophasic levonorgestrel (with 30 mcg EE) in a total of 817 women followed for 6 cycles. Results were similar with regard to reasons for discontinuation, adverse effects, spotting/breakthrough bleeding, and absence of withdrawal bleeding. There were no pregnancies. One trial reported less intermenstrual bleeding with gestodene (RR 0.71, 95% CI 0.55-0.91).
- *3rd vs. 1st generation progestogens* – there were three trials comparing third- vs. first-generation progestogens, two triphasics and one monophasic (total 976 women). Adverse effects, breakthrough bleeding, and discontinuations were similar between groups.

- *2nd vs. 1st generation progestogens* – there were six trials comparing levonorgestrel or norgestrel to norethindrone or norethisterone (2709 women receiving monophasic preparations and 581 triphasic. Pregnancies occurred in one of two trials reporting pregnancy rates; more pregnancies occurred in the 1st generation group (RR 0.12, 95% CI 0.02-0.99) over a 1-year period. In the monophasic group, fewer women receiving second-generation products discontinued (RR 0.76, 95% CI 0.67-0.86). Adverse effects and discontinuations due to adverse effects were similar. Second-generation progestogens appeared to be associated with better cycle control for both monophasic (RR: 0.69, 95% CI: 0.52-0.91) and triphasic (RR: 0.61, 95% CI: 0.43-0.85) products.
- *Within generation comparisons* – Seven studies (5624 women) compared the third-generation gestodene- vs. desogestrel-containing monophasic products. Results were comparable, although more women receiving gestodene-containing products discontinued due to non-cycle-related adverse effects (RR 1.81, 95% CI 1.01-3.23). One study reported similar results (discontinuations, reasons for discontinuation, and overall adverse effects) for the third-generation gestodene- vs. norgestimate-containing products (174 women over 6 months).
- *Drospirenone* – Two trials compared drospirenone- vs. desogestrel-containing products (2985 women total; 13-26 months). Pregnancy rates, adverse effect rates, and discontinuations due to adverse effects were similar between groups.

Authors noted the following:

- There was no clinically relevant difference in contraceptive effectiveness among the different progestogens, with failure rates in 1-year or longer trials ranging from 0.2 to 1.8%.
- In trials involving monophasic products, the overall discontinuation rate ranged from 8.2% to 17.9% in trials lasting 6 cycles and 25.5% to 28.7% for trials lasting 12 cycles. Discontinuation rates with second-generation products were higher than with third-generation products, but lower than first-generation products.
- Authors were unable to combine results on spotting and breakthrough bleeding per cycle without distorting the data, since spotting and/or breakthrough bleeding may occur not only during several cycles, but also several times during a single cycle. An incidental finding based on one trial comparing product containing gestodene and either 15 mcg or 20 mcg EE was a higher rate of breakthrough bleeding in the 15 mcg EE group (RR 1.67, (95% CI, 1.00-2.95), possibly related to the lower EE content.
- The trials have major shortcomings, including small size and lack of information about randomization, blinding (4 trials were "double-blinded" but details were lacking), and other measures of acceptability (e.g., satisfaction with treatment).
- Overall, third- and second-generation progestogens appear preferable to first-generation progestogens. The comparison between third- and second-generation progestogens is unclear. Drospirenone appears similar to the third-generation product desogestrel.

Rosenberg et al (1992)[15] evaluated 25 studies assessing cycle control with various OCs. In general, products containing norgestrel and levonorgestrel (2nd generation products) were found to cause a lower incidence of spotting and breakthrough bleeding compared with norethindrone acetate and norethindrone (1st generation), whether triphasic or monophasic.

Two trials comparing two norethindrone-containing triphasic products vs. a levonorgestrel-containing triphasic product found that the levonorgestrel product was associated with a lower rate of intermenstrual bleeding.[16, 17]

Biphasic and triphasic products & cycle control

It is not clear whether biphasic and triphasic regimens offer any clinically meaningful advantage over monophasic OCs, although overall reduction in progestogen and/or estrogen exposure should be related to a decrease in thromboembolic events.

As reported by Mishell (1991),[3] use of the older type of biphasic (two levels of progestogen) declined relative to triphasic products because of a suggested increase in breakthrough bleeding. In a Cochrane

review last updated in 2005, Van Vliet et al compared biphasic with triphasic OCs in terms of efficacy, cycle control, and discontinuation due to side effects.[18] Only two trials met inclusion criteria. One trial found similar results with two biphasic OCs and one triphasic OC (all containing levonorgestrel/EE) [19]. The other compared a biphasic OC containing norethindrone (Ortho 10/11) with a triphasic OC containing levonorgestrel (Triphasil) and another containing norethindrone (Ortho 7/7/7).[20] The biphasic product had inferior cycle control compared to the levonorgestrel triphasic product, based on differences in cycles with intermenstrual bleeding (OR 1.7, 95% CI 1.3-2.2) and cycles without withdrawal bleeding (OR 6.5, 95% CI 3.1-13). On the other hand, the biphasic product had comparable results to the triphasic product with the same progestogen. After making allowances for the poor quality of the evidence, authors concluded that cycle control may depend more on choice of progestogen than the phasic regimen.

Extended/continuous use & cycle control

Five products are specifically approved and packaged for extended use or continuous use. Clinically, many products are used in 3-month or longer cycles or on a continuous basis. This practice was initially investigated for treatment of endometriosis, dysmenorrhea, or menstruation-related symptoms, but has expanded to support extended or continuous use based on personal preference.

- *Cochrane review* - In a Cochrane review last updated in 2005, Edelman et al[21] reviewed randomized controlled clinical trials (1966 – 2005) using extended or continuous combined OCs. The six trials that met inclusion criteria [22-27] included a number of different formulations and extended cycle lengths (ranging from 49 days for four cycles to 365 days). Overall, the studies were too small to address efficacy, rare adverse events, and safety, and too dissimilar to combine results in a meta-analysis.

  With respect to bleeding patterns, most of the included trials either showed no difference between groups or less bleeding/spotting with extended/continuous dosing. Study discontinuation was lower in the traditional 28-day cycle group in one study [27] (OR 1.6; 95% CI 1.2-2.3), but otherwise did not differ between groups. Two studies reported significantly fewer discontinuations due to bleeding problems with extended/continuous use.[24, 27] Three trials that collected adherence data reported no differences between groups.[22, 23, 27] In three studies reporting menstruation-related symptoms, one reported a significant decrease in headache frequency with extended use,[24] a second reported less severe genital irritation, headache, and tiredness in the 49-day cycle group,[23] and a third reported significantly less bloating and menstrual pain in the 168-day cycle group.[26] In the two studies that monitored endometrial thickness,[22, 26] all measurements were less than 5 mm, the cut-off value of concern for abnormal pathology in postmenopausal women. Authors concluded that extended/continuous dosing of combined OCs is reasonable for women without contraindications.

- While not a randomized trial, Sillem et al, 2003[28] reported results of an observational study that followed 1433 women, 175 of whom took Yasmin continuously for 42-126 days. Of the 1433 women, 668 (47%) were new users of OCs, while 765 (53%) were changing from another product. Women were questioned at baseline and 6 months about changes in swelling of extremities, body weight, breast tenderness, feeling of bloating, skin condition, dysmenorrhea, breakthrough bleeding, and withdrawal bleeding. In general, both new users and switchers reported improvement on most of these measures, with greater improvement among extended regimen users.

24-day cycle & cycle control

Two products offer a 24-day on, 4-day off cycle (Yaz, Loestrin 24 Fe). Rationale for this approach has been offered by a number of authors.[29-34] Potential beneficial effects include decreased follicle development during the off-cycle (which may result in bleeding when OCs are resumed); a wider safety margin (since ovulation may occur if women delay restarting OCs after the off cycle and since 20 mcg EE products may theoretically decrease contraceptive effectiveness); and reduction of adverse effects occurring during the off-cycle. It should be noted that, like extended and continuous use regimens, the same regimen may be achieved by throwing away the last 3 pills in a conventional OC pack and starting the new pack early.

Heavy menstrual bleeding and dysmenorrhea (menstrual pain)

Dysmenorrhea is a common complaint, affecting up to 50% of women (10% severely).[35] Combined OCs have been used to treat dysmenorrhea since their introduction in 1960. It is defined as primary (associated with ovulatory cycles and with no organic pathology) or secondary (associated with a condition such as endometriosis or ovarian cysts). By suppressing ovulation and lessening the endometrial lining of the uterus, combined OCs reduce the amount of prostaglandins produced, reducing dysmenorrhea by decreasing uterine motility / cramping. Regular shedding of a thinner endometrial lining also reduces the likelihood of heavy menstrual bleeding (i.e., greater than 80 mL per period).

Clinical trials supporting the effectiveness of combined OCs in treating dysmenorrhea include an open trial of 661 women[36] (after 12 months of treatment 12% of women still experience dysmenorrhea vs. 63% pretreatment) and an open trial of a low dose combined OC involving 100,000 women[37] (65% of first time users of oral contraceptives with pre-existing dysmenorrhea experienced relief).

In a Cochrane review last updated in 2004,[38] Proctor et al reviewed randomized controlled trials comparing combined OCs with other combined OCs, placebo, no treatment, or treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of primary dysmenorrhea. Outcome measures included pain relief, adverse effects, additional analgesics required, and time lost from work or school. A total of 5 trials were included; 4 of these were combined in a meta-analysis. All of the trials included combined OCs with > 35 mcg of estrogen (80 mcg of mestranol in two trials, 50 mcg mestranol in one trial, and 50 mcg of estrogen in two trials) and first- or second-generation progestogens, compared to placebo. Meta-analysis results showed the combined OCs to be more effective than placebo for pain relief (Peto OR 2.01, 95% CI 1.22-3.33), although the difference was non-significant when reanalyzed using a random effects models to compensate for significant heterogeneity within the trials (OR 1.68, 95% CI 0.29-9.81). Not surprisingly, adverse effects were higher in the combined OC group, although this outcome was reported by only two studies. One study reported a significant reduction in women reporting absences from work or school with combined OC therapy.

As the authors rightly point out, conclusions about the efficacy of currently used combined OCs, which use lower estrogen doses, cannot be drawn from these studies.

In a Cochrane review last updated in 2004, [39] Iyer et al reviewed available literature in an attempt to determine the effectiveness, adverse effects, and cost-effectiveness of combined OCs vs. other treatments in reducing menorrhagia, but found only one small cross-over study comparing mefenamic acid, naproxen, low dose danazole, and a combined OC. There were no differences between the groups; women taking combined OCs had a 43% reduction in menstrual blood loss, although the number of women was very small (n=6).

Acne

Acne is a common skin condition related to an increased rate of sebum production, predominantly controlled by androgenic sex hormones. Combined OCs may prevent acne through several mechanisms: suppressing leutinizing hormone, causing decreased production of androgens, including free testosterone; increasing the level of sex hormone-binding globulin, causing increased binding of testosterone; and blocking androgen receptors and inhibiting activity of the enzyme that converts testosterone to dihydrotestosterone in the hair follicles and skin. Progestogens appear to vary in their effects on testosterone production, availability, or conversion to dihydrotestoterone.[40]

In a Cochrane review last updated in 2005,52 Arowojolu et al reviewed a total of 21 trials: 5 placebo-controlled trials (3 different comparisons), 14 trials comparing two combined OC regimens (9 different comparisons), and 1 trial comparing a combined OC to an antibiotic. It should be noted that, in the UK, the combined OC licensed and traditionally used for acne treatment contains 35 mcg EE and 2 mg of cyproterone acetate, a progestogen not available in the U.S. In the U.S., the combined OC with FDA approval for acne is EE 35 mcg / norgestimate 180-215-250 mcg (Ortho Tri-Cyclen), which is now generically available.

The *five placebo-controlled trials* included two trials with EE 20 mcg/levonorgestrel 100 mg, one with EE 20-30-35 / norethindrone acetate 1 mg, and two with EE 35 mcg / norgestimate 180-215-250 mcg. [41-45] All five trials showed improvements in acne in women receiving the combined OC.
Head-to-head comparisons - Results from comparisons involving products with progestogens not available in the U.S. (e.g., cyproterone, chlormadinone, gestodene) are not summarized here. Unfortunately, this leaves only three trials. Two trials comparing EE 30 mcg / levonorgestrel 150 mcg to EE 30 mcg / desogestrel 150 mcg reported a small difference in mean acne severity score favoring levonorgestrel in one trial, but no difference in mean total lesion count in the other.[46,47] The third found no differences in acne outcomes between EE 20 mcg / levonorgestrel 100 mcg and EE 20 mcg/norethindrone 1 mg.[48]
The one trial that compared a combined OC vs. an antibiotic did not find differences in acne improvement or discontinuation rates. However, this trial was small, flawed, and utilized a product not available in the U.S.

Overall, authors found conflicting or negative evidence regarding differences in combined OCs other than cyproterone and chlormadione.

There are a number of trials evaluating drospirenone-containing OCs for the treatment of acne. Van Vloten et al (2002)[49] compared 30 mcg EE/3 mg drospirenone (Yasmin) to a combined OC containing 35 mcg EE/2 mg cyproterone (not available in the U.S., but used elsewhere for contraception/acne treatment). Yasmin was at least as good as the comparator, with a greater decrease in median total acne lesion count after 9 cycles (62.5% with Yasmin; 58.8% with the comparator). In a double-blind study, Thorneycroft et al (2004)[50] compared Yasmin to a triphasic OC (Ortho Tri-Cyclen) containing 35 mcg EE and varying amounts of norgestimate, the OC most widely associated in the U.S. with acne treatment. Patients were randomized to Yasmin (n=568) or Ortho Tri-Cyclen for six 21-day on, 7-day off treatment cycles. Yasmin was superior for reduction in total lesion count (-3.3% in favor of Yasmin [95% CI, -6.5 to -0.1; P = 0.020]) and for investigators' assessment of therapeutic effect on facial acne (+3.6% in favor of Yasmin [95% CI, 0.8 to 6.3; P = 0.006]). The products were comparable with respect to decreases in inflammatory lesion count.

The manufacturer provided data on two unpublished, double-blind, randomized 6-month trials concentrating on the effect of the newer drospirenone-containing product, Yaz, on acne. In both trials, Yaz was superior to placebo in the mean percent change from baseline on all 3 primary acne efficacy measures and the probability that skin was “clear” or “almost clear” on an investigator-rated global scale.

Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)

Premenstrual Syndrome (PMS) occurs during the luteal phase of the menstrual cycle (after ovulation but prior to menstruation) and is defined as symptoms severe enough to interfere with work or relationships, resolving with or soon after the start of menstruation. The etiology is unclear and the symptoms varied; PMS may in reality be several different conditions with different causes. Common symptoms include bloating, breast tenderness, exhaustion and joint pain, but also anxiety, irritability, depression and mood swings (which are somewhat hard to reconcile with a single cause). Treatment for PMS may be symptomatic (e.g., diuretics for bloating, antidepressants for mood swings); aimed at stopping the menstrual cycle and therefore the associated symptoms (e.g., extended or continuous cycle contraceptives), or based on presumed causes.

One presumed cause involves progesterone. Since symptoms occur during the luteal phase when progesterone levels are high, they may be related to a lower than normal ratio of progesterone to other hormones (e.g., water retention caused by insufficient progesterone to oppose estrogen). This does not appear to be related to a simple deficiency, but may be related to the frequency and pattern of release of progesterone and luteinizing hormone.[51]

Premenstrual dysphoric disorder (PMDD) is a form of PMS sufficiently severe to carry its own DSM-IV diagnosis; it is typically treated with antidepressants.

The progestogen drospirenone is a derivative of spironolactone that binds to aldosterone receptors, causing excretion of excess sodium and water in exchange for potassium, thus reducing bloating, breast tenderness, and weight gain. Thus drospirenone-containing OCs may be expected to have a beneficial effect on the physical symptoms of PMS and PMDD.

The efficacy of the newest drospirenone product, Yaz, in treating PMDD has been assessed in two randomized, placebo-controlled trials. Yonkers et al (2005)[52] randomized a total of 450 women to either placebo or Yaz, given for 3 cycles following 2 run-in cycles. PMDD symptoms were assessed based on the Daily Record of Severity of Problems (DRSP) scale, which consists of 24 questions grouped into 11 distinct symptom items and 3 functional impairment items, self-rated on a 6-point scale from 1 [not at all] to 6 [extreme]). Averages of the last 5 days before menses for the 11 distinct symptom items are summed to derive the total DRSP symptom score. DRSP total score decreased by –37.5 in the Yaz group vs. –30.0 in the placebo group (adjusted mean difference (AMD) -7.5, 95% CI -11.2 to -3.8; $P \leq 0.001$). Mood symptoms were reduced by -19.2 with Yaz vs. -15.3 with placebo (AMD -3.9, 95% CI -5.84 to -2.01; $P \leq 0.003$); physical symptom scores by -10.7 vs. -8.6 (AMD -2.1, 95% CI -3.3 to -0.95; $P \leq 0.001$); and behavioral symptom scores by -7.7 vs. -6.2 (AMD -1.5, 95% CI -2.251 to -0.727; $P \leq 0.001$). Response, defined as a 50% decrease in daily symptom scores, occurred in 48% of the active treatment group and 36% of the placebo group (relative risk 1.7, 95% CI 1.1 to 2.6; $P \leq 0.015$), corresponding to a number-needed-to-treat of 8. A smaller placebo-controlled crossover trial reported by Pearlstein et al (2005)[53] reported similar results, with a significantly greater mean decrease from baseline in total DRSP scores for Yaz (-12.47, 95% CI -18.28, -6.66; $p \leq 0.001$) and a higher percent of patients with a positive response, (a score of 1 or 2 on the Clinical Global Impressions-Improvement scale): 61.7% with Yaz vs. 31.8% with placebo ($p = 0.009$).

Pain associated with endometriosis

Endometriosis occurs when excess endometrial tissue implants in other areas of the body (e.g., ovaries, fallopian tubes, and other organs in the pelvic region). Symptoms include dysmenorrhea, dyspareunia (painful sex), and pelvic or lower abdominal pain. It is treated surgically and/or with hormonal drugs, including OCs or gonadotropin-releasing hormone agonists (GnRH agonists) such as leuprolide. Since symptoms apparently resolve during pregnancy, high dose combinations of estrogens and progestogens were initially used to simulate pregnancy, followed by progestogens alone. Since high doses of estrogen and progesterone are now seldom used, modern options include low dose OCs and injectable DMPA.

The evidence for combined OCs in the treatment of endometriosis pain is not definitive. In a Cochrane review last updated in 2004,[54] Moore et al reviewed trials assessing the effectiveness, adverse effects, compliance, and cost-effectiveness of combined OCs for the treatment of painful symptoms associated with the diagnosis of endometriosis, compared to placebo, no treatment, other medical therapies, or conservative surgical treatment. However, only a single trial, comparing a combined OC and a GnRH analog, met inclusion criteria. The combined OC was less effective in relieving dysmenorrhea; no difference was noted regarding relief of dyspareunia or non-menstrual pain. Adverse effects varied based on treatment option. The authors concluded that the limited data supports use of combined OCs for pain associated with endometriosis, but more research is needed.

Safety / Tolerability

Serious Adverse Events / Contraindications

Use of combined OCs is associated with increased risk of several serious conditions, including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although absolute risk is very low in women without risk factors. Much of the epidemiological data was obtained from studies using oral contraceptive formulations containing higher estrogen and progestogen doses than currently used. The effect of long-term, low dose OC use has yet to be determined.

Absolute contraindications to the use of combined OCs include:

- Previous thromboembolic event or stroke, cerebral vascular or coronary artery disease, or valvular heart disease with complications
- Major surgery with prolonged immobilization
- Severe hypertension
- Headaches with focal neurologic symptoms
- Known or suspected estrogen-dependent tumor (e.g., endometrial, breast cancer)
- Liver disease
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use

- Pregnancy
- Undiagnosed abnormal uterine bleeding
- Women over age 35 years who smoke

Relative contraindications, which should be considered in individual cases or may require dose adjustment, include:

- Obesity – Women with a BMI > 27 may be at increased risk of pregnancy if prescribed low dose estrogen formulations. However, since obesity is an independent risk factor for thromboembolism, use of higher estrogen formulations (50 mcg) is not advisable.
- Inherited thrombophilias - Combined hormonal contraceptives should be avoided, although routine screening is not recommended
- Poorly controlled hypertension – risk of exacerbation
- Treatment with anticonvulsants – efficacy may be reduced due to drug interactions
- Migraine headaches, especially with classic migraine – possible increased risk of stroke
- Diabetes – not a contraindication if no vascular disease is present, but insulin dose may need to be increased

Thromboembolism

Case control studies have found the relative risk of thromboembolism in users vs. nonusers of combined OCs to be 3 for the first episode of superficial venous thrombosis, 4-11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions. Cohort studies have shown relative risks of about 3 for new cases and 4.5 for new cases requiring hospitalization. Risk is not related to duration of use and returns to baseline when use is stopped.

A 2004 review by Gomes et al (2004) [55] summarizes the evidence regarding combined OCs and the risk of venous thromboembolism (VTE). He notes that:

- Since 1995, 13 of 15 studies have found greater VTE risk in users of 3rd generation combined OC compared to 2nd generation, although the difference is not always statistically significant.
- Some studies classify norgestimate, which is partially metabolized into levonorgestrel, as 2nd generation; the risk of VTE with norgestimate appears similar to levonorgestrel and lower than desogestrel and gestodene, based on limited data.
- There has been fierce controversy concerning potential bias and confounding in epidemiological studies; however, independent reviews conclude that biases may partially account for, but do not seem to entirely explain, the difference in risk. Two meta-analyses have concluded that it is small but real.
- Most available data is with monophasic products; data is limited for biphasics and triphasics.

Epidemiological data for drospirenone is not yet available. Some debate concerning a theoretical increase in risk exists, although the argument does not appear to be well-advanced as yet. A 2004 safety review of drosperinone-containing products[56] reported 3-year interim results from a large, controlled, postmarketing surveillance study suggesting a VTE rate of 61 per 100,000 women-years, similar to 60/100,000 women-years reported for levonorgestrel products and 73/100,000 women-years for other OCs. The study reported a worldwide spontaneous VTE reporting rate of 5.1/100,000 women-years for drospirenone/EE use.

Cardiovascular and cerebral vascular disease (Myocardial infarction and stroke)

An increased risk of myocardial infarction (MI) has been associated with OC use, primarily in smokers or women with underlying risk factors for coronary artery disease. As expressed in contraceptive labeling, the relative risk of MI in current users of combined OCs is estimated to be 2 to 6. The risk is very low for women younger than 30, but increases markedly with age, even in non-smokers. Smoking substantially increases risk, especially in women over 35. Combined OCs have been shown to increase the risk of thrombotic and hemorrhagic strokes, with the greatest risk among hypertensive women > 35 who also smoke. It is important to note, however, that the evidence summarized in labeling is based on higher doses of estrogen than are currently in use.

In a 2005 meta-analysis, Baillargeon et al[57] reviewed the risk of cardiovascular diseases associated with low dose OCs. A total of 14 studies were included in the meta-analysis. Summary risk estimates associated with current use of low-dose OCs were 1.84 (95% CI 1.38 to 2.44] for MIs and 2.12 (95% CI 1.56 to 2.86) for ischemic strokes. The summary odds ratio for MI or ischemic stroke was 2.01 (95% CI 1.63 to 2.48). In a sub-group analysis based on type of progestogen, second generation OCs were associated with a significant increased risk of both MI and ischemic stroke [1.85 (95% CI 1.03 to 3.32) and 2.54 (95% CI 1.96 to 3.28), respectively]. Third-generation OCs significantly increased risk of ischemic stroke only [2.03 (95% CI 1.15 to 3.57)], with a non-significant increase in the risk of MI (28%).

Chan et al (2004)[58] systematically reviewed the risk of stroke with low-dose OCs. The analysis included 20 study populations (4 cohort and 16 case-control studies). While the pooled odds ratio from the case-control studies was significantly increased (2.13; 95% CI 1.59-2.86; P< 0.001), the same was not true in the cohort studies. Reviewers noted statistically significant heterogeneity among studies and potential biases and confounding factors that were not adequately addressed. They concluded that the association between low-dose OCs and stroke was “tenuous at best and perhaps nonexistent."

Cancer

Current and recent users of combined OCs may have a slightly increased risk of having breast cancer diagnosed, but breast cancers are typically at an earlier stage than in non-users. The excess risk appears to be gone by 10 years post discontinuation of combined OCs. Evidence is insufficient to establish a causative relationship between combined OCs and cervical cancer.

Other serious adverse events

Benign hepatic adenomas have been associated with OC use, although the risk is in the range of 3.3 cases per 100,000 users. Studies have also shown an increased risk of hepatocellular carcinoma, but estimates of attributable risk in the US are less than 1 in 1,000,000 users. Case reports of retinal thrombosis have been reported with OCs.

Overall Adverse Effect Profile

In general, adverse effects of oral, transdermal, or vaginal ring oral contraceptives may include: breast tenderness, headache, migraine, nausea, nervousness, vomiting, dizziness, weight gain, tiredness, decline of libido, and increased blood pressure. While it is not always possible to attribute an adverse effect to either the estrogen or progestogen component, estrogen-related adverse effects may include nausea, vomiting, headaches, breast tenderness, and changes in body weight; progestogen side effects may include acne, weight gain, increased hair growth, and depression.

Specific adverse effects

Fluid retention/bloating& weight gain

Since EE can increase aldosterone and other mineralocorticoids, the fluid retention and abdominal bloating associated with combined contraceptive products is thought to be related to stimulation of the renin-aldosterone system by estrogen. Endogenous progesterone has a natriuretic effect, which counteracts the sodium and water retention caused by estrogen. This does not appear to be the case with most progestogens used in combined OCs, with the exception of drospirenone. A 3 mg drospirenone dose appears to have the same antimineralocorticoid effects as 25 mg of spironolactone.

Drospirenone has been shown to reduce fluid retention[59, 60] and may avoid some of the cyclical weight fluctuations that occur with most combined OCs. In a large long-term trial (26 cycles; n=900) comparing EE 30 mcg/drospirenone 3 mg (Yasmin) to a comparator OC containing EE 30 mcg/150 mcg desogestrel, Foidart et al (2000)[61] reported statistically different differences in mean body weight between groups. Patients receiving the desogestrel product had decreases in mean body weight during cycles 1-5, but increases from cycle 7 on. Patients receiving Yasmin had slight decreases in body weight throughout the treatment period, except in cycles 25 & 26. A similar 1-year study (n=2069) using the same comparator (Huber et al, 2000)[61] reported decreases in both groups, but a statistically significantly greater loss for Yasmin over the treatment period.

Hyperkalemia

The anti-mineralocorticoid properties of drospirenone may be of concern in patients with conditions that predispose to hyperkalemia or receiving medications that can increase potassium. Labeling recommends that women receiving daily, long-term treatment with medications that can increase potassium should have their serum potassium levels checked during the first treatment cycle. While precautions are indicated, there is little evidence (e.g., no case reports in Medline) to suggest serious concern, given that about 14 million women worldwide have received Yasmin, according to the manufacturer.

Blood pressure

Increases in blood pressure are known to occur in women taking OCs. A 1989 World Health Organization (WHO) study[62] comparing 704 women younger than 35 using a combined OC (EE 50 mcg/levonorgestrel 250 mcg) to 703 women using a non-hormonal intra-uterine device (IUD), reported higher systolic and diastolic blood pressures among those receiving the OC. Data from the Nurses' Health Study[63] has shown a relative risk of approximately 1.8 for development of hypertension in women receiving low dose combined OCs. Increasing progestogen doses were associated with a higher risk of hypertension; the lowest risk occurred in women receiving triphasic OCs, which have the lowest total progestogen dose.

In a recent systematic review, Curtis et al (2006)[64] addressed the use of combined OC use among women with hypertension. Based on 25 included trials, authors concluded that hypertensive users of combined OCs were at higher risk for stroke and acute MI than hypertensive non-users, but that they were not at higher risk for venous thromboembolism (VTE). Data from two studies suggested that women with hypertension on combined OCs may have further increases in blood pressure, but reviewers found these studies to be of low quality. Women who did not have their blood pressure measured before starting combined OCs were at higher risk for ischemic stroke and AMI than those who had a blood pressure measurement, although the same was not true for hemorrhagic stroke or VTE.

Progestogen-only OCs do not appear to significantly increase blood pressure. A 2003 systematic review[65] included four studies in normotensive women treated with progestogen-only OCs, three prospective control trials and one cross-sectional survey. The author reported no significant association of high blood pressure with use of progestogen-only OCs for up to 2-3 years.

Metabolic effects (carbohydrates and lipids)

Decreases in HDL cholesterol have been reported with many progestogens. Since estrogens increase HDL, the net effect depends on the balance between estrogen and progestogen doses and the amount and activity of the progestogen. Changes in serum triglyceride levels have been reported with combined OC use.

Combined OCs may decrease glucose tolerance in some users, but appear to have no effect on fasting plasma glucose in non-diabetics.

Headaches

Onset or exacerbation of migraine or a new pattern of recurrent, persistent, or severe headaches should lead to discontinuation of OCs and evaluation of the cause. Women with menstrual migraines may benefit from extended or continuous treatment with oral contraceptives.

Other effects

Combined contraceptives may worsen gallbladder disease.

Safety in lactation

Postpartum women who exclusively breastfeed, are within 6 months of delivery, and have not restarted menses are unlikely to ovulate and are at low risk for pregnancy. However, return of menstruation and ovulation can be unpredictable, making the timing of initiating contraception important. During pregnancy, prolactin levels rise, but are suppressed by estrogen and progesterone. After delivery, levels of estrogen and progesterone drop, allowing prolactin to initiate milk production (sustained by further stimulation of prolactin triggered by infant suckling). Contraceptive choices may be limited by concerns regarding the quantity and quality of milk and hormonal effects on the infant. Progestogen-only OCs may be less problematic than combined OCs; however, women tend to prefer combined OCs.

A Cochrane review last updated in 2005[66] addressed the effect of combined and progestogen-only OCs on lactation. A total of seven reports from five randomized controlled trials (one trial contributed three

comparisons) met inclusion criteria. Overall, results of the two trials comparing combined OCs to placebo were conflicting (and flawed by lack of quantifiable outcomes); one trial comparing progestogen-only OCs to placebo showed no effect on milk volume, milk composition, or infant growth; timing of progestogen-only contraception initiation assessed in one trial (6 weeks vs. 6 months or resumption of menses) did not affect continuation rates or pregnancy rates; and one trial reported an statistically significant decline in milk volume with combined OCs vs. progestogen-only OCs. Authors conclude that the evidence is insufficient to make recommendations regarding hormonal contraceptive use in lactation.

Hormonal contraceptives are Pregnancy Category X.

Other special populations

There are a number of special populations in whom combined contraceptive therapy offers increased, and in some causes unacceptable, risk (e.g., smokers > 35 years of age, women with a history of DVT, women over 40), or in whom a particular choice of OC may be more desirable (breast-feeding, endometriosis).

Drug interactions

A number of medications may interact with hormonal contraceptives. Some antibiotics, antifungals, anticonvulsants, and other drugs (e.g., barbiturates, griseofulvin, rifampin, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, St. John's Wort, and possibly ampicillin and tetracyclines) increase metabolism of contraceptive hormones, increasing the risk of pregnancy. Anti-HIV protease inhibitors may also cause significant changes in estrogen and progestogen levels. Atorvastatin appears to increase area-under-the-curve (AUC) for EE by about 20%. Ascorbic acid, acetaminophen, and CYP3A4 inhibitors (e.g., ketoconazole) may also increase EE and/or progestogen levels.

Oral contraceptive may increase levels of cyclosporine, prednisolone, and theophylline and decrease levels of acetaminophen, temazepam, salicylic acid, morphine, and clofibrate.

Conclusions

Combined OCs– The number of potential variables that could influence the choice of a combined contraceptive product is large and the relationships among these variable are complex. The estrogen, progestogen, and androgenic effects of a particular product may impact the risk of serious adverse events (e.g., VTE), non-contraceptive benefits, and adverse effects, although there is little evidence of substantial differences in contraceptive effectiveness. Differences in regimens (e.g., extended or continuous use, 24-day cycles) may affect compliance and satisfaction with therapy, as well as the incidence of adverse effects and practical issues associated with reducing or eliminating menstrual periods.

Progestogen-only OCs – Progestogen-only OCs have a well-defined place in therapy, with some trade-offs compared to the combined OCs. There are no competing formulations; the six brand or branded generic products all contain 0.35 mg of norethindrone and do not differ in dosing regimen.

Emergency contraception – Emergency contraception is highly effective in preventing pregnancy when given shortly after unprotected intercourse. Societal issues with emergency contraception appear to be mainly related to either its mechanism of action or its availability (e.g., to certain groups, in specific venues, in advance of use).

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