

Table 1: Benefits & Risks ^{1,2,11}

Benefits:

- ◆Simple and highly effective
- ◆Reduces need for sterilization & abortion
- ◆**Significantly improves menstrual symptoms®ularity**
 - ◆Reduces dysmenorrhea and mittelschmerz
 - ◆Reduces menstrual blood loss (up to 50%)
 - ◆Reduces risk of anemia
 - ◆Reduces PMS
 - ◆Alleviates menorrhagia/hot flashes in perimenopausal ♀
- ◆**Decreases incidence of disease**
 - ◆bacterial pelvic inflammatory disease (60%)
 - ◆ectopic pregnancy
 - ◆endometriosis
 - ◆*endometrial cancer (>50%)
 - ◆*ovarian cancer (>40%)
 - ◆ovarian cysts (>60%)
 - ◆acne and hirsutism
 - ◆fibrocystic breast disease (50-75%)
 - ◆osteoporosis
 - ◆rheumatoid arthritis (50%)

* benefit greatest with long term use (>5yr) and persists up to 15 yrs after discontinuing

Risks:

- ◆**venous thromboembolism** = ↑ 3-4x with low dose OCs and possibly further ↑ 1.7x with new progestins (estrogens ↓ activation of Protein C so ↑ risk of thrombus)^{3,4,5}
- ◆**arterial thrombosis** (myocardial infarction and stroke) - related to estrogen dose ≥50 ug, age >35, smoking, hypertension, and other risk factors for CVD (↑~2-3x); otherwise no ↑ risk over baseline in young non-smoking ♀⁶
- ◆**breast cancer** = ↑ 1.3x ?; women who started OCs at early age for long duration at greatest risk; persists for <10yrs after d/c (also related to nulliparity/delay in childbearing)
- ◆**cervical cancer** = ↑ 1.5x with long term use (>5yr)⁷; also related to early sexual activity & multiple partners
- ◆**gall bladder disease** = ↑ 1.5x during 1st 5yrs of OC use
- ◆does **not** protect against sexually transmitted diseases (**STDs**)
- ◆may exacerbate and/or precipitate: hypertension, diabetes, gallbladder and liver disease, SLE, migraine headaches, depression, GERD, vaginal yeast infections
- ◆failure esp. if missed doses with 20ug estrogen formulations

Tables adapted from RxFiles newsletter – *Hormonal Contraception* – Jan 00

Drug causes of OC failure: alcohol -excessive chronic, **antibiotics** (ampicillin, cotrimoxazole, griseofulvin, metronidazole, nitrofurantoin, neomycin, penicillin, rifabutin, rifampin & tetracycline), **anticonvulsants** (carbamazepine, ethosuximide, oxcarbazepine, phenobarbital, phenytoin, primidone & topiramate ^{↑dose}), **antivirals** (nelfinavir & ritonavir), modafinil, red clover & St. John's wort.

Table 2: Contraindications and Precautions ¹

Contraindications:

- ◆**active thromboembolic disease**
- ◆**undiagnosed vaginal bleeding**
- ◆**acute or chronic obstructive liver disease**
- ◆**known or suspected breast cancer**
- ◆**known or suspected pregnancy**

Precautions :

- ◆**Hypertension** - may use OCs if hypertension controlled
- ◆**CVD, hyperlipidemia**- OCs with new progestins preferred because of more favorable lipid profile
- ◆**Diabetes** - low dose OCs unlikely to affect glucose control but estrogen may complicate vascular disease
- ◆**Epilepsy** - some anticonvulsants ↓ OCs efficacy due to ↑ metabolism; may require use of OCs with >35ug EE
- ◆**Hepatitis, cirrhosis** - avoid OCs if active disease; may use if liver enzymes have returned to normal
- ◆**Gallbladder disease** - may be exacerbated by OCs
- ◆**Migraine** - avoid OCs if classic, complex, age ≥35 (↑stroke)
- ◆**Inflammatory bowel disease** - active diarrhea may reduce absorption and efficacy of OCs and require backup method
- ◆**Systemic lupus erythematosus** - avoid OCs as estrogens can complicate vascular disease
- ◆**Smoking women over age 35** - if light smoker (<15cigs/day) or on nicotine patch, can use 20 ug EE product but ↑ risk

Table 3: Starting Hormonal Contraceptives

Starting Combined OCs:

- ◆**most effective if started Day 1 of menstrual period**
- ◆can be started any day up to Day 6
- ◆to avoid weekend period, start on 1st Sunday after period begin
- ◆**if started after Day 5 use backup method for first 7 -10 days** as ovulation may not be suppressed

Starting Progestin-only Pill (POP): irregular bleeding common

- ◆start on Day 1 of menstrual period and daily thereafter
- ◆use backup method for first month
- ◆take pills at the same time each day to ↓ BTB & pregnancy¹¹

Starting Depo-Provera®:

- ◆should be injected during the first 5 days of menstrual cycle to rule out pregnancy
- ◆repeat injection q12 weeks - effective for up to 14 wks
- ◆return of fertility delayed 4-31 (median 10) months after last inj¹¹

Starting Norplant®: {Note: Norplant no longer made in Canada}

- ◆insert within the first 7 days of menstrual cycle to rule out pregnancy
- ◆must be removed and replaced after 5 yrs

Table 4: ACHES - OCs Early Danger Signs ⁸

SIGN	PROBLEM
Abdominal pain (severe)	Gallbladder disease, pancreatitis, hepatic adenoma, thrombosis
Chest pain (severe), SOB	Pulmonary embolus or acute MI
Headaches (severe)	Stroke, hypertension, migraine
Eye problems - blurred vision, flashing lights, blindness	Stroke, hypertension, vascular insufficiency
Severe leg pain (calf or thigh)	Deep vein thrombosis (DVT)

Table 5: Side Effects & Their Management ^{1,9}

- ◆**Breakthru bleeding (BTB)** -most common in 1st 3 months; if persists beyond 3-6mon check for other causes (eg. chlamydia). Change to OC with ↑ estrogen/progestin depending on when BTB occurs in the cycle; may also be related to poor compliance, smoking, DIs
- ◆**Breast tenderness** - if persists beyond 1st 3months rule out pathologic causes; change to OC with ↓ estrogen/progestin
- ◆**Weight gain** - may ↑ appetite in 1st month but overall weight gain is minimal with low dose OCs & within normal limits for age-related gain; may be cyclical due to Na & H₂O retention
- ◆**Nausea** - often subsides within 3 months; take at hs with food or change to lower estrogen content
- ◆**Headache** - tension headaches unaffected but hormone related or vascular migraines may ↑↓; if precipitated or exacerbated by OCs should avoid their use
- ◆**Acne** - sometimes worsens initially but usually improves in the long term; change to ↓ androgenic OC or use topical therapy
- ◆**Chloasma** - irreversible and idiosyncratic; exacerbated by sunlight so use sunscreen and reduce exposure; ↓ estrogen dose

References:

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3. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1995; 346: 1575-82
4. Effect of different progestagens in low estrogen oral contraceptives on venous thromboembolic disease. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1995; 346: 1582-8.
5. Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. BMJ. 2001 Jul 21;323(7305):131-4.
6. Acute myocardial infarction and combined oral contraceptives: results of international multicentre case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1997; 349: 1202-9
7. Schlesselman J. Net effect of oral contraceptive use in risk or cancer in women in United States. Obstet Gynecol. 1995; 85: 793-801.
8. Hatcher R et al. Contraceptive Technology, 16th edition. New York, Irvington, 1994.
9. Dickey R. *Managing Oral Contraceptive Patients*, 9th edition. Essential Medical Information Systems, Durant, OK. 1998.
10. Petitti, Diana B. Combo Estrogen-Progestin Oral Contraceptives. NEJM 2003;349:1443-1450.
11. Treatment Guidelines: Choice of Contraceptives. Medical Letter: Aug, 2004; p. 55-62.



BRAND NAME	COMPONENTS	Hormonal Activity			\$ Cost (12mon)	
		E	P	A		
Oral Contraceptives (OC)						
1 st Generation	MINESTRIN 1/20	Ethinyl estradiol 20 ug Norethindrone 1 mg	+	+++	+++	209
	LOESTRIN 1.5/30	Ethinyl estradiol 30 ug Norethindrone 1.5 mg	+	+++	++++	209
	DEMULEN 30	Ethinyl estradiol 30 ug Ethinodiol diacetate 2 mg	+	++++	+++	228
	BREVICON 0.5/35	Ethinyl estradiol 35 ug Norethindrone 0.5 mg	+++	+	+	201
	ORTHO 0.5/35	Ethinyl estradiol 35 ug Norethindrone 0.5 mg x12; 1mg x 9tab	+++	++	++	213
	SYNPHASIC (Biphasic)	Ethinyl estradiol 35 ug Norethindrone 0.5 mg x12; 1mg x 9tab	+++	++	++	188
	BREVICON 1/35, ORTHO 1/35, SELECT 1/35	Ethinyl estradiol 35 ug Norethindrone 1mg	+++	+++	+++	201-213 SELECT 150
	ORTHO-NOVUM 1/50 (21 tablet package only)	Mestranol 50 ug Norethindrone 1mg	+++	+++	+++	213
	ORTHO 7/7/7 (Triphasic)	Ethinyl estradiol 35 ug Norethindrone 0.5 - 0.75 - 1 mg	++++	++	++	213 {7 tabs of each in sequence}
2 nd Generation	ALESSE	Ethinyl estradiol 20 ug Levonorgestrel 0.1 mg	+	+	++	210
	TRIQUILAR, TRIPHASIL (Triphasic)	Ethinyl estradiol 30 - 40 - 30 ug Levonorgestrel 0.05 - 0.075 - 0.125 mg	++	+	++	196 210 {7 tabs of each in sequence}
	MIN-OVRAL	Ethinyl estradiol 30 ug Levonorgestrel 0.15 mg	++	++	+++	210
	OVRAL	Ethinyl estradiol 50 ug Norgestrel 0.25 mg	+++	+++	++++	210
3 rd Generation	MARVELON, ORTHO-CEPT	Ethinyl estradiol 30 ug Desogestrel 0.15 mg	++	+++	+	210
	CYCLEN	Ethinyl estradiol 35 ug Norgestimate 0.25 mg	+++	+	+	213
	TRI-CYCLEN (Triphasic)	Ethinyl estradiol 35 ug Norgestimate 0.18 - 0.215 - 0.25 mg	+++	+	+	213 {7 tabs of each in sequence}

♦venous thromboembolism: slight ↑ risk, esp. with desogestrel (16 vs 6 cases/100,000 ♀/year, age 20-24) BMJ 2001;323:131-4; NEJM 2003;349:1443-50.

New Ways and Means... Contraception: what's new.; Pharmacy Practice May 2003

Extended Dosing of OC's:

- ♦**Bi-cycling or Tri-cycling** refers to taking 2-3 consecutive packages of active pills (ie 42-63 days) followed by a week off for menstruation (menses is no different than with traditional dosing)
- ♦method appears safe & effective
- ♦**Advantages:** ↓ in menses and associated symptoms
- ♦A **monophasic** product must be used since the bi- and tri-phases can cause spotting. ♦Currently **SEASONALE (84 day pill pack)** is approved in the USA Sep'03

New Products:

- ♦**MIRCETTE** ^{xNA} = 28day pill pack with 21 active tabs followed by 2 placebo tabs ; then 5 tabs of estradiol 10ug (↓ risk of missing first active pills of 21day cycle with ultra low dose products)
 - ♦**EVRA TRANS-DERMAL PATCH** ^{x®} releases 20ug estradiol + 150ug norelgestromin daily; 1 patch weekly x3 weeks; off for one week ; can be used consecutively for 9 weeks, 1 week off Cost ~\$400/year
 - ♦**NUVARING** ^{xNA} releases estradiol 15ug + etonogestrel 120ug daily; insert vaginally for 3 weeks, then remove for 1 week
 - ♦**MIRENA Intrauterine System** is a T-shaped IUD with a levonorgestrel reservoir that releases 20ug daily and last up to 5yrs. Decreases menstrual periods (frequency & duration); 20% of users amenhoric within 1st year. Fertility returns immediately after removal. (\$350/5yrs)
 - ♦**IMPLANON** ^{xNA} = **NORPLANT** ^{DC'd Aug02} reformulated into single rod system that releases 60ug etonogestrol daily. Effective for up to 3yrs. Amenorrhea in 20% of users within 1st year
 - ♦**LUNELLE** ^{xNA} (avail. USA) is a monthly injection of estradiol cypionate (5mg) with medroxy-progesterone (25mg); rapid return to fertility
 - ♦**YASMIN** ^{xNA} (new OC available in the USA) contains a new progestin, drospirenone (spironolactone derivative) 3mg + estradiol 30ug per tab; advantages = less weight gain (diuretic effect?) & ↓ breakthru bleeding
- NA= not yet available in Canada**

Product Selection guided by Signs & Symptoms of...

Estrogen Deficiency	Progestin Deficiency	Estrogen Excess +/- Progestin Deficiency	Excess Estrogen	Excess Progestin	Excess Androgen	ACNE
<ul style="list-style-type: none"> ♦early bleeding & spotting days 1-9 ♦continuous bleeding or spotting ♦decrease in flow ♦absence of withdrawal bleeding ♦pelvic relaxation symptoms ♦atrophic vaginitis ♦vasomotor symptoms ♦nervousness 	<ul style="list-style-type: none"> ♦late bleeding and spotting days 10-21 ♦delayed withdrawal bleeding 	<ul style="list-style-type: none"> ♦PMS ♦bloating, edema ♦headache (cyclic) ♦dizziness ♦irritability ♦nausea, vomiting ♦visual changes (cyclic) ♦weight gain (cyclic) ♦leg cramps ♦dysmenorrhea ♦hypermenorrhea, menorrhagia 	<ul style="list-style-type: none"> ♦hypermenorrhea, clotting, menorrhagia ♦dysmenorrhea ♦UTI ♦↑ breast size or cystic changes ♦mucorrhea ♦cervical ectrophy ♦uterine enlargement or fibroid growth ♦thromboembolism ♦hypertension ♦vascular headaches ♦chloasma 	<ul style="list-style-type: none"> ♦depression ♦fatigue ♦libido decrease ♦weight gain (non-cyclic) ♦↑ appetite ♦symptoms of hypoglycemia ♦leg vein dilation ♦hypertension ♦cervicitis ♦yeast infection 	<ul style="list-style-type: none"> ♦libido increase ♦oily skin / scalp ♦acne ♦rash & pruritus ♦hirsutism ♦edema ♦cholestatic jaundice 	<ul style="list-style-type: none"> ♦All OCs likely beneficial in acne - due to estrogen binding to sex hormone binding globulin (SHBG) ♦ Official Acne Indication ALESSE, TRI-CYCLEN & DIANE 35 ^{x▼} (ethinyl estradiol 35ug + cyproterone 2mg; Health Canada Apr03 warning: - not for contraception only; discontinue within 4 months of resolution of acne; Cost \$345 / 12 packs)

Cost =total 1yr cost in Sask. ✕ =non-formulary Sask. ▼ covered NIHB Note: both 21 & 28 tablet packages avail. for most products (28 packages incl. 7 inert tablets) **Progestin Only: Levonorgestrel PLAN B** 0.75mg tab -indicated for emergency contraception. **Norethindrone MICRONOR** 0.35mg tab -indicated in ♀ with contraindication or intolerance to estrogen, venousthromboembolism history or migraine, **post-partum/lactating** & in **smokers**; \$213/yr. **Medroxyprogesterone (MPA) DEPO-PROVERA** 150mg/1ml for deep **IM Inj q3 months**; 1st dose injected in the first 5 days cycle; repeat injections at ~12 week intervals (dose is effective for up to 14 weeks); \$150/yr. **Diane 35**: officially indicated for women with severe acne, unresponsive to oral antibiotic & other available treatments, with associated symptoms of androgenization, including seborrhea and mild hirsutism. **References:** 1. Biological activity and therapeutic management. OC Chart. Organon Canada Ltd. 1997. 2. Dickey R. *Managing Oral Contraceptive Patients*, 9th edition. Essential Medical Information Systems, Durant, OK. 1998. 3. Product monographs. 4. www.RxFiles.ca-Jan00.