Prescribing Oral Contraceptive: The Standard of Care

Vivien Brown MDCM, CCFP, FCFP, NCMP
Department of Family & Community Medicine
University of Toronto
Author

Vivien Brown, MDCM, CCFP, FCFP, NCMP
Department of Family & Community Medicine
University of Toronto
Toronto, Ontario
Disclosure

• Unrestricted educational grant from Merck, Bayer
• Travel, honorarium from Bayer, Novartis, Pfizer, Amgen, Merck, GSK
After This Session Learners Will be Able to:

- Describe contraceptive and non-contraceptive benefits of combined OCs.
- Discuss the evolution of the pill with regard to thrombogenic risk: understand and interpret the current conflicting data
- Discuss appropriate patient selection for the pill and how to counsel a patient
- How to maintain standard of care in prescribing oral contraceptive
What did we learn in the last 50 years….
“Love, Sex, Freedom and the Paradox of the Pill”

“Arriving at a moment of social and political upheaval, the Pill became a handy proxy for wider trends: the rejection of tradition, the challenge to institutions, the redefinition of women’s roles”

Nancy Gibbs,
Time Executive Editor
Contraception Improves Women’s Welfare

- Life satisfaction data collected in 450,000 women
- Biggest contributor to an increase in “life satisfaction” was access to contraception, because it increases:
  - Investment in education
  - Probability of working
  - Level of income

Pezzini, Economic Journal 2005
Most Commonly Used Contraceptive Methods by Canadian Women

Column totals may exceed 100% as women were allowed to choose more than one method.
Base: Women aged 15-50 who have had vaginal intercourse in the previous 6 months, n=2,341

A New Tool For Your Practice

SOGC CLINICAL PRACTICE GUIDELINE

Oral Contraceptives and the Risk of Venous Thromboembolism: An Update

This clinical practice guideline has been reviewed by the Clinical Practice Gynaecology Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHOR
Robert Reid, MD, Kingston, ON

contraceptives, hormonal contraception. Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. Searches were updated on a regular basis and incorporated in the guideline to May 2010. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international

Summary Statements

1. COCs are highly effective contraception with a range of non-contraceptive benefits

2. VTE, although rare, remains one of the serious adverse consequences of hormonal contraception

3. COCs with $\leq 35\mu g$ of EE carry a lower risk of VTE than COCs with $50\mu g$

4. Contradictory evidence and the ensuing media coverage have led to fear and confusion about the safety of COCs

5. Research studies found comparable VTE rates with DRSP-containing COCs and other approved products

6. Other reports suggesting an increased risk of VTE with DRSP-containing COCs have significant methodological flaws

Oral Contraceptives and the Risk of Venous Thromboembolism: An Update

Summary Statement #1

- Modern oral contraceptives offer highly effective contraception and a range of non-contraceptive benefits.

Unintended Pregnancy in First Year of Contraceptive Use*

*not head-to-head comparison of contraceptive methods

COC=combined oral contraceptive; POP= progestin only pill; DMPA=depot medroxyprogesterone; LNG-IUS=levonorgestrel releasing intrauterine system

Trussell J. Contraception 2004; 70: 89-96.
Risk of Not Using an Effective Contraception

- Unintended pregnancy

  Did you know?
  85% of young women who have intercourse without using birth control will get pregnant within one year

- Abortion

  Did you know?
  A total of 96,815 induced abortions were performed on Canadian women in 2005

Trussell J. Contraception 2004; 70: 89-96.
Statisitic Canada, Catalogue no. 82-223-X 2005
# Maternal Mortality Ratio
Canada (excluding Quebec), 1997-2000

<table>
<thead>
<tr>
<th>Age</th>
<th>Maternal Mortality Ratio per 100,000 Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 years</td>
<td>3.2</td>
</tr>
<tr>
<td>20-24 years</td>
<td>2.1</td>
</tr>
<tr>
<td>25-29 years</td>
<td>5.0</td>
</tr>
<tr>
<td>30-34 years</td>
<td>7.6</td>
</tr>
<tr>
<td>35-39 years</td>
<td>10.5</td>
</tr>
<tr>
<td>40 years and older</td>
<td>12.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6.1</strong></td>
</tr>
</tbody>
</table>

Occurrence of Severe Maternal Morbidity in Canada*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate per 1,000 deliveries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amniotic fluid embolism (AFE)</td>
<td>0.06</td>
</tr>
<tr>
<td>Obstetrical pulmonary embolism (not incl. AFE)</td>
<td>0.16</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>0.38</td>
</tr>
<tr>
<td>Shock (obstetrical, septic and other)</td>
<td>0.33</td>
</tr>
<tr>
<td>Pulmonary, cardiac and CNS complications of anaesthesia</td>
<td>0.49</td>
</tr>
<tr>
<td>Cerebrovascular disorders in the puerperium (including intra-cranial venous sinus thrombosis)</td>
<td>0.16</td>
</tr>
<tr>
<td>Uterine rupture</td>
<td>0.74</td>
</tr>
<tr>
<td>Adult respiratory distress syndrome</td>
<td>0.08</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0.16</td>
</tr>
<tr>
<td>Myocardial infraction</td>
<td>0.01</td>
</tr>
<tr>
<td>Acute renal failure following labour and delivery</td>
<td>0.09</td>
</tr>
<tr>
<td>Cardiac arrest/ failure or cerebral anoxia following obstetrical surgery</td>
<td>1.05</td>
</tr>
<tr>
<td>Post-partum hemorrhage requiring hysterectomy</td>
<td>0.35</td>
</tr>
<tr>
<td>Post-partum hemorrhage requiring transfusion</td>
<td>0.91</td>
</tr>
<tr>
<td>Post-partum hemorrhage requiring hysterectomy or transfusion</td>
<td>1.22</td>
</tr>
<tr>
<td>Assisted transfusion</td>
<td>0.15</td>
</tr>
<tr>
<td>Delivering women with one or more conditions</td>
<td>4.62</td>
</tr>
</tbody>
</table>

Noncontraceptive Uses of Hormonal Contraceptives

Box 1. Potential Noncontraceptive Benefits of Hormonal Contraception

- Menstrual cycle regularity
- Treatment of menorrhagia
- Treatment of dysmenorrhea
- Inducing amenorrhea for lifestyle considerations
- Treatment of premenstrual syndrome
- Prevention of menstrual migraines
- Decrease in risk of endometrial cancer, ovarian cancer, and colorectal cancer
- Treatment of acne or hirsutism
- Improved bone mineral density
- Treatment of bleeding due to leiomyomas
- Treatment of pelvic pain due to endometriosis

Reid R., Obstet Gynecol 2010; 115(1): 206-218
The Combined OC: Benefits Beyond Reliable Contraception

Short term benefits
- Cycle regulation and decreased menstrual flow
- Decreased dysmenorrhea, premenstrual syndrome, acne & hirsutism

Long term benefits
- Decreased risk of endometrial & ovarian cancer
- Possibly fewer cases of benign breast disease

Other benefits
- Decreased incidence of acute PID and ectopic pregnancy
- Possibly fewer ovarian cysts
- Potential benefits on endometriosis

Yaz Product Monograph, Bayer Inc. June 3, 2010
VTE, although rare, remains one of the serious adverse consequences of hormonal contraception

Best evidence indicates that venous thromboembolism rates are:

<table>
<thead>
<tr>
<th>Category</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-users of reproductive age</td>
<td>4–5 / 10 000 woman/years</td>
</tr>
<tr>
<td>Oral contraceptive users</td>
<td>9–10 / 10 000 woman/years</td>
</tr>
<tr>
<td>During pregnancy</td>
<td>29 / 10 000 woman/years</td>
</tr>
<tr>
<td>In the immediate postpartum period</td>
<td>300–400 / 10 000 woman/years</td>
</tr>
</tbody>
</table>

Understanding Risk: Cardiovascular Adverse Events

Most serious cardiovascular adverse events associated with all COCs

- Venous thromboembolism
- Stroke
- Myocardial infarction

Farley et al., Contraception 1996; 57(3)211-30
The Risk of VTE During COC Use

- **CLASS EFFECT:** the risk of VTE is increased during COC use compared with no use
- The risk of VTE during COC use is lower than during pregnancy and child birth
- It has been known since the 1960’s that COC use is associated with an increased risk of VTE
- The risk of VTE has always been associated with the dose of the estrogen component

Putting the VTE Risk into Context

Ten Thousand Women Years:

Non-pregnant women not using any EE containing COCs (4.4/10,000 women-years)

Women using low dose EE containing COCs (8.9/10,000 women-years)

Pregnant women (29.5/10,000 women-years)

Dinger et al., Contraception 2007; 75(5):344-54
Putting the Risk of VTE Into Perspective

Risk increasing

Very Rare Event
- VTE in non-pregnant, non-users
- VTE in COC users
- VTE in pregnancy and delivery
- Sustaining injury in a car accident
- Major gastrointestinal tract bleeding in NSAID users

Rare Event

Uncommon Event

Common Event

1 in 1 Million
1 in 100,000
1 in 10,000
1 in 1,000
1 in 100
1 in 10
1 in 1
Risk Assessment

The World Health Organization (WHO) has developed a list of absolute and relative contraindications to the use of combined OCs, based on the available evidence of risks.

Do we know the difference between Absolute Risk and Relative Risk?
COCs Absolute Contraindications

- < 6 weeks postpartum if breastfeeding
- Smoker over the age of 35 (≥ 15 cigarettes per day)
- Hypertension (systolic ≥ 160mm Hg or diastolic ≥ 100mm Hg)
- Current or past history of venous thromboembolism (VTE)
- Ischemic heart disease
- History of cerebrovascular accident
- Complicated valvular heart disease (pulmonary hypertension, atrial fibrillation, history of subacute bacterial endocarditis)
- Migraine headache with focal neurological symptoms
- Breast cancer (current)
- Diabetes with retinopathy/nephropathy/neuropathy
- Severe cirrhosis
- Liver tumour (adenoma or hepatoma)

COCs Relative Contraindications

- Smoker over the age of 35 (< 15 cigarettes per day)
- Adequately controlled hypertension
- Hypertension (systolic 140–159mm Hg, diastolic 90–99mm Hg)
- Migraine headache over the age of 35
- Currently symptomatic gallbladder disease
- Mild cirrhosis
- History of combined OC-related cholestasis
- Users of medications that may interfere with combined OC metabolism

Risk Assessment – Standard of Care

- Risk factor information is important in deciding whether a COC is a suitable contraceptive choice for an individual woman.
- For the vast majority of those who use COCs, the benefit-risk profile is favourable when used as indicated.
Risk Factors for Thromboembolism

Risk Factors include but not limited to:

- Use of estrogen and progestin combinations
- Age
- Severe obesity (BMI >30 kg/m²)
- Family and personal history of VTE / ATE
- Systemic lupus erythematosus
- Prolonged immobilization, major surgery, or trauma
- varicose veins and leg cast
- Smoking
- Dyslipoproteinemia, hypertension, migraine, valvular heart disease, and atrial fibrillation
Increased Impact of Age and BMI on VTE Incidence in COC Users*

*Risk estimates based on 115 VTEs in 116,708 WY of exposure
Dinger, EURAS Study, Presentation EC Prague 2008
VTE Risk Greatest in First Year of COC Use

- Numerous observational studies have demonstrated an increased risk of VTE in the first year of use of COCs or menopausal HT.
- A possible explanation is that this hormonal “challenge”, like pregnancy, unmasks a propensity to VTE in women with an underlying thrombophilia.
- Restarting — following a 4-week or greater pill-free interval — the same or a different COC also lead to an increased risk of VTE.

Suissa S et al., Contraception 1997; 56:141-146
Dinger JC et al., Contraception 2007; 75:344-354
Duration of Use Impacts VTE Risk

VTE Incidence vs. Duration of Use

Dinger et al., Contraception 2007; 75:344-354
Research demonstrates that COCs with ≤35 µg of EE carry a lower risk of VTE than COCs with 50 µg.

Although preliminary data suggest a possible further reduction in VTE with COCs with < 35 µg EE, robust data to support this conclusion are presently lacking.
Reduction in Estrogen Dose Over Time

Oral contraceptives containing mestranol
Oral contraceptives containing ethinyl estradiol

What Drove the Movement to Lower Estrogen Doses?

- High rates of discontinuation rates due to AEs
- Concern about estrogen-related safety issues:
  - Breast cancer
  - Cerebrovascular complications
  - Thromboembolic incidents
  - Myocardial infarction
- Discovery that estrogen and progestin act synergistically to inhibit ovulation, thus lower doses may be equally effective

Effect of Decreasing Estrogen Dosages in COC’s

- Fewer estrogen related side effects: nausea, breast tenderness, headache
- Potential for more breakthrough bleeding with <35 ug EE
- VTE risk:
  - 30-35 ug cause less VTE than 50 ug COCs in some head-to-head comparative trials
  - No evidence that <20 ug pills are safer than >20 ug pills

Gallo et al., Contraception. 71(3):162-9, 2005
Recent contradictory evidence and the ensuing media coverage of the VTE attributed to the progestin component of certain newer COC products have led to fear and confusion about the safety of COC in general and drospirenone-containing COC in particular.

“Pill scares” of this nature have occurred in the past, with panic stopping of the pill, increased rates of unplanned pregnancy, and no subsequent decrease in VTE rates.

Impact of the Media
UK Example During 1990s

- Widespread media reports on increased risk of blood clots in women using a popular new oral contraceptive
- Women panicked and stopped taking the pill resulting in many thousands of unplanned pregnancies
- 9 months later, London hospitals reported:
  - 25% more deliveries
  - an additional 10,000 women sought pregnancy termination
  - no subsequent decrease in VTE

2 high quality research studies that addressed the VTE risk associated with various COC found comparable VTE rates with drospirenone-containing COC and other approved products.

Rate Ratio

VTE rate ratio for study group vs. control group

**Rate Ratio:** chance of events occurring in the treatment arm as a ratio of the chance of the events occurring in the control arm.
Incidence Rate: the number of new cases per population in a given time period.

Incidence per 10,000 woman/years (95% CI)

- **Product A**: n=1,000
- **Product B**: n=1,000
- **Product C**: n=300

Point Estimate: narrow range
Overlapping CI: no statistical difference

Wide confidence Interval (CI)
EURAS: Large Active Surveillance Study

Objectives:
- Powered to evaluate VTE risk between different progestins in COCs

Population:
- Followed 58,674 new users (140,000 woman years)

Design:
- Large, independently-conducted, prospective, observational study
- **Setting**: Europe
EURAS: VTE Rate Ratio

DRSP-COCs* vs. Other COCs

* DRSP-COC: 30 µg EE / 3 mg drospirenone in 21/7 regimen
Dinger Contraception 2007; 75(5):344-354
EURAS: Incidence of VTE

Incidence per 10,000 woman/years (95% CI)

- **DRSP-COC**: 30 µg EE / 3 mg drospirenone in 21/7 regimen
- **LNG-COC**: n=15,428
- **Other-COC**: n=26,341

*Dinger Contraception 2007; 75(5):344-354*
INGENIX: Large Prospective Study

Objectives:
- Compare DRSP/EE thromboembolic events to other COCs

Method:
- Used propensity (risk factor) scoring system to match users of different pills according to baseline VTE risk

Design:
- Large, prospective, controlled cohort database study

Setting: USA

Seeger Obst & Gyn. 2007; 110(3):587-593
INGENIX: VTE Rate Ratio

DRSP-COCs* vs. Other COCs

VTE Rate Ratio
ITT Analysis (95%CI)

* DRSP-COC: 30 µg EE / 3 mg drospirenone in 21/7 regimen
Seeger Obst & Gyn. 2007; 110(3):587-593
Summary Statement #6

- 2 reports suggesting an increased risk of VTE with drospirenone-containing COC have significant methodological flaws that render their conclusions suspect.

- It seems likely that residual confounding could have distorted both the results and the conclusions of these reports.

Controlling for Potential Biases and Confounding Factors in COC and VTE Studies

Are you comparing similar populations?

- Is the proportion of high-risk patients different?
- Duration of use: short-term versus long-term users?
- Preferential prescribing to high-risk users: is the distribution of high-risk patients similar?
Dutch MEGA Case-Control Study

Objectives:
- Investigate risk factors for VTE and to assess the risk of thrombosis associated with the combination of risk factors

Analysis:
- Post-hoc sub-analysis to evaluate the thrombotic risk associated with COC use in women aged 18–50 years

Design:
- Large, population-based, case-control study of VTE cases

Setting: The Netherlands

Van Vlieg, BMJ 2009; 339: b2921
Dutch MEGA Case-Control Study Author’s Conclusions

1. The risk of VTE was positively associated with estrogen dose

2. A higher risk of VTE was confirmed during the first months of COC use irrespective of the type of oral contraceptives

3. The risk clearly differed by type of progestin

Van Vlieg, BMJ 2009; 339: b2921
Dutch MEGA Case-Control Study
Results

Adapted from Van Vlieg, BMJ 2009
Danish Cohort Study

Design:
- Retrospective national database cohort study following all reproductive-aged women in Denmark from 1995 to 2005

Method:
- Linking of national exposure and event databases

Exposure data:
- Redeemed prescription data for COCs

Event data:
- All first-time VTE events (hospital discharge diagnoses)

Lidegaard BMJ 2009; 339: b2890
Author’s Conclusions
Danish cohort study

- The risk of venous thrombosis in current users of COC decreases with duration of use and by decreasing oestrogen dose.

- For the same dose of oestrogen and the same length of use, COC with desogestrel, gestodene, or drospirenone were associated with a significantly higher risk of VTE than COC with levonorgestrel.

Lidegaard BMJ 2009; 339: b2890
Lidegaard et al: Study Limitation

Major questions about the cohort comparisons for VTE risk include:

- No information of COC use prior to 1995, thus cannot account for exact duration of use
- No information available regarding confounders (eg, obesity)
- VTEs in registry database could only be confirmed in:
  - 31% diagnoses from ER
  - 71% diagnoses from wards

Reid, J Fam Plann Reprod Health Care 2010
Severinsen, J. of Clinical Epidemiology, 2010
Rate Ratio of Venous Thromboembolism According to Duration of Use

Rate Ratio of venous thromboembolism with non-users of COC as reference group

Duration of Use (years)

Lidegaard BMJ 2009; 339: b2890
Potential Misclassification of Duration of Use in LNG-COC Users in the Danish Cohort Study

Incorrectly classified as short term users

Correctly classified as short term users


Study Start

DRSP/EE COC* launch

* DRSP/EE COC: 30 µg EE / 3 mg drospirenone in 21/7 regimen
FDA Conclusion on the 4 Studies

- **Two prospective cohort studies** (EURAS\(^1\), Ingenix\(^2\)) showed the risk of thromboembolism (particularly VTE) and death in Yasmin users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel.

- Two additional epidemiological studies, **one case-control study\(^3\) and one retrospective cohort study\(^4\)** suggested that the risk of VTE occurring in Yasmin users was higher than that for users of levonorgestrel containing COCs and lower than that for users of desogestrel/gestodene-containing COCs.
  - In the case-control study, the number of Yasmin cases was very small (1.2% of all cases) making the risk estimates unreliable.
  - The relative risk for Yasmin users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of Yasmin to that for users of other COC products.

---

Retrospective Nested Case-Control Studies

Objective:
- Compare the risk of VTE in DRSP-containing COC users to LNG-containing COC users

Design:
- Nested control-studies based on
  - UK General Practice Research Database
  - USA claims data

Results:
- COC containing-DRSP carries a higher risk of VTE than do formulation containing-levonorgestrel

Study limitations:
- Retrospective studies have significant methodological issues inherent to their study design

GPRD: General Practice Research Database
Parkin et al., BMJ 2011;340:d2139
Jick and Hernandez et al., BMJ 2011;340:b2151
Retrospectives Studies - Limitations

- Lack of validation of VTE cases
- Lack of information on important potential confounders such as duration of use, family history, body mass index (BMI) and smoking
- Data on duration of exposure to all contraceptives may not be reliable
- Prescriber bias towards newer COCs
- Poor matching of cases and controls

Summary Statements

1. COCs are highly effective contraception with a range of non-contraceptive benefits

2. VTE, although rare, remains one of the serious adverse consequences of hormonal contraception

3. COCs with $\leq 35\mu g$ of EE carry a lower risk of VTE than COCs with $50\mu g$

4. Contradictory evidence and the ensuing media coverage have led to fear and confusion about the safety of COCs

5. Research studies found comparable VTE rates with DRSP-containing COCs and other approved products

6. Other reports suggesting an increased risk of VTE with DRSP-containing COCs have significant methodological flaws

Standard of Care

How do You Counsel
Your Patients on Oral Contraceptive
Clinician Considerations for Contraception

- Contraindications or safety concerns
- Side-effect profile
- Potential for consistent/correct use
- Non-contraceptive benefits
- Appropriate & Inappropriate work-up
  - PAP smears: not mandatory
  - Routine screening of thrombogenic mutations - e.g. Factor V Leiden
    - Not appropriate because of the rarity of the conditions and the high cost of screening

WHO, Medical eligibility and criteria for contraceptive use, 2009
Pill Talk With Your Doc

Pill Talk With Your Doc Webcast

Understanding the risks
Patient Considerations for Contraception

- Hormonal vs. non-hormonal
- Daily or nondaily
- Side effects/safety profile
- Efficacy
  - Typical use (effectiveness)
- Perceptions/misperceptions of methods
- Future childbearing plans
  - If she wants children, when and how many?
  - Would she terminate an unintended pregnancy?
Patient Counselling

- Instructions on how to take the combined OC
- Information on potential side-effects
- Non-contraceptive benefits of the combined OC
- Addressing common myths and misconceptions
- Discussing risks and warning signs, including when to seek medical care
- Discussing what to do if pills are missed
- Emphasizing dual protection (the combined OC with condom use to prevent STIs and HIV infection)
- Information about emergency contraception in the event of missed pills

Canadian Contraception Consensus, JOGC 2004
Reinforce Adherence

- Many women underestimate the number of pills that they miss each cycle.

- Developing a relationship with the patient and being available to answer questions can facilitate method adherence.

- Clinicians may be able to identify potential impediments for consistent use and adherence, such as ambivalence or major life changes.

Frost and Darroch, Perspect Sex Reprod. Health 2008; 40 (2):94-104
VTE Risk and COC Use

- The risk for venous and arterial events **is rare** in COC users.
- The VTE risk **is comparable** for all modern low EE-dose COCs.
- The risk for blood clots is **lower than the risk during pregnancy/delivery**.
- Risk factors (**age and weight**) increase the risk of VTE in COC users.
- Risk factors (**age, hypertension and tobacco use**) increase the risk for myocardial infarction and stroke in COC users.
Pearls

- Contraception counselling is an individual assessment. We need to do that appropriately.

- Patients have access to a lot of information but also a lot of misinformation. Health Care Professionals need to read articles critically to understand conflicting data.

- Appropriate and current guidelines are available. We need to use them.
Questions?