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YAZ / YASMIN: Safety Considerations related to Venous Thromboembolism (VTE)

Bottom Line: **The use of CHCs increases a woman's risk of VTE relative to non-users; however the estimated absolute risk for users of any type of CHC is very low and even lower than the risk during pregnancy and postpartum. Recent scientific focus has been placed on estimating the risk of VTE associated with the use of drospirenone (DRSP), i.e. Yaz & Yasmin, relative to older progestins. *Small, observed differences* in VTE risk have been reported among different progestins, suggesting the estimated risk may be slightly higher with DRSP compared to levonorgestrel. Some experts feel it is prudent for most women to first consider a contraceptive containing levonorgestrel or norethindrone, with as low a dose of estrogen as possible, given the well known favourable safety profile. As well, few women have a specific indication that may benefit from the use of DRSP 1st line (eg, hirsutism). Consider individual patient factors when discussing the benefits and risks associated with CHCs.**

(Refer to Appendix Table 4: Risk Factors for VTE & RxFiles Hormonal Contraception - Supplementary Tables for list of contraindications http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-OCs-Color.pdf**)**

What is Yaz / Yasmin? Which products are available in Canada?

- CHCs containing the hormones ethinyl estradiol & drospirenone.
- Health Canada approved indications are conception control and the treatment of moderate acne vulgaris.
- Additional FDA indication for Yaz: treatment of the emotional & physical symptoms of premenstrual dysphoric disorder (PMDD).

Table 1: CHCs containing drospirenone that are available in Canada

Product name	Drospirenone	Ethinyl Estradiol	Pills per Cycle
Yasmin - 21	3 mg	0.03 mg	21 d on, 7 day off
Yasmin - 28	3 mg	0.03 mg	21 d on, 7 day hormone-free tablet
Yaz	3 mg	0.02 mg	24 d on, 4 day hormone-free tablet

What is drospirenone?[1]

- Drospirenone is frequently referred to as a **4th generation progestin**. It is the first synthetic progestin not derived from a sex hormone. Instead, it is chemically related to spironolactone and possesses **antimineralocorticoid** and **antiandrogenic** activity (3 mg DRSP is comparable to 25 mg spironolactone).[2]

What has sparked public concern over the safety of Yaz / Yasmin?

- In 2008 the FDA warned the manufacturer of Yaz about **misleading marketing**. One concern was the **minimizing of important risks** in drug marketing.[3] In response, Bayer released less distracting ads to help viewers better understand the potential for serious adverse effects, such as VTE. (USA)
- A **myriad of lawsuits** against Bayer USA & Canada have mounted in the past few years. A central theme is that Bayer allegedly did not adequately warn women of the greater risk for serious side effects by taking Yaz/Yasmin as compared to other CHCs.
- The Society of Obstetricians and Gynaecologists of Canada (SOGC) suggests the **rash of adverse event reporting** to Health Canada related to these CHCs likely represents "stimulated reporting" as a result of increased **media attention**.

What is a typical woman's risk for VTE?

- VTE is an uncommon condition in young, healthy, non-pregnant women.
- All types of CHCs are associated with a small increase in the risk of VTE compared with no use.

Table 2: Absolute risk of VTE per 10,000 women per year (estimated) [4]

Non-CHC users	4 to 5 in 10,000
CHC users	8 to 9 in 10,000
Pregnancy (may be as high as 300 to 400 / 10,000 in immediate post-partum period)	29 in 10,000

CHC= combined hormonal contraceptives **VTE**=venous thromboembolism

Refer to RxFiles Chart "Contraceptive, Combination Hormonal Products - Prescription" for complete listing of products. http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-OCs-Color.pdf

What do we know about drospirenone (DRSP) and the risk of VTE?

- The thromboembolic risk of DRSP relative to other progestins continues to be debated; best available evidence is limited to few prospective trials and several retrospective, database studies. Expert debate is mainly focused over the significance of reported findings and the validity of conclusions reached.
- Of note, none of the published studies to date have reported a significantly ↓risk of VTE for DRSP compared to LNG.
- Points for consideration regarding methodological limitations: small #'s of VTE cases make risk estimates more unreliable, misclassification of a long- versus short-term CHC user, lack of control for confounders (e.g. +ve family history of VTE, BMI & lifestyle factors), patient self-reporting of VTE versus diagnostic parameters. In addition, CHCs increase VTE risk maximally during the 1st months of use, after which the risk declines. The inclusion of 1st year data may be considered a confounder for this reason, and may explain higher VTE rates reported for recently marketed OCPs time and time again ('pill scares').
- **Whether the small observed difference in ↑ risk for DRSP represents a true difference is questionable due to low-quality, observational evidence.**

- Preliminary data from a FDA-funded study are consistent with an *approximately 1.5-fold increase in the risk* of blood clots for users of DRSP-containing CHCs compared to users of other CHCs. In this study, VTE risk was about 6 in 10,000 in CHC users and 10 in 10,000 in women using Yasmin. However, this is a retrospective database study with limited validation of VTE and accounting for confounders known to impact the risk of VTE.[5] It **is important to keep risk estimates in perspective!!**

Table 3: A look at the observations... **{as with all observational research, the ability to infer causation is limited}**

Pub Yr	Cohort	Sample sizes	Results	Comments
2005	UK	n=15,645 [6]	-cases of VTE associated with use of Yasmin; incidence rate of 13.7 cases per 10,000 woman-years ($CI_{95\%}$ 7.3-23.4)	-rate was considered an overestimate due to selective prescribing & non-response bias -national Rx event monitoring study
2007	Europe & USA	EURAS[7] n=58,674 f/u: 1.5-5 yrs INGENIX[8] n=67,287 f/u: 7 mo (avg)	-investigated the RR of VTE in women using DRSP containing CHCs compared to women using other progestin containing CHCs -there was a comparable risk of VTE in Yasmin users compared to users of other CHCs , including LNG (HR 0.9 ($CI_{95\%}$ 0.6-1.4) and RR 0.9 ($CI_{95\%}$ 0.5-1.6))	-2 large, prospective, controlled cohort studies, industry sponsored - adjusted for age, BMI, duration of use, VTE history in EURAS; propensity score matching in INGENIX - VTE events adjudicated
2009	Netherlands & Denmark	MEGA[9] n=3,284 Danish[10] 4,213 events	- MEGA: not statistically significant for the comparison of DRSP and LNG (OR 1.7 (0.7-3.9) - Danish: OR 1.64 (1.27-2.10)	- both studies suggested the risk of VTE in Yasmin users was slightly higher than previously thought, but databases with incomplete data used
2010	Germany	680 events[11]	-2˚ outcome found no evidence of ↑ VTE risk among users of DRSP containing CHCs compared to LNG	-case-controlled study, industry sponsored
2011	USA & UK	186 cases/681 controls [21] & 61 cases/215 controls [22]	-higher VTE risk with DRSP containing CHCs compared to LNG; risk estimates were slightly higher than the 2009 studies -UK: adj. OR 3.3 ($CI_{95\%}$ 1.4-7.6), 2.3 vs 0.9 per 10,000 yrs -USA: OR 2.3 ($CI_{95\%}$ 1.6-3.2), 3.1 vs 1.3 per 10,000 yrs	-2 small, independent case-controlled studies - had much lower than usual estimated risk, suggesting incomplete data
2011	Denmark (re-analysis)	n=1.3 million; ~8 million ♀-yrs of observation 4,307 events[23]	-compared to LNG and adjusted for length of use, the rate ratio {relative} for confirmed VTE cases for DRSP was 2.1 ($CI_{95\%}$1.6-2.8) - ~2,000 ♀ would need to be switched from CHCs containing a newer progestin to a CHC containing LNG to prevent 1 case of VTE (assuming the absolute risk of VTE in users of "newer progestins" is ~ 10/10 000 ♀-yrs)	-data linkage; focus post-DRSP launch -analysis funded by manufacturer - incomplete VTE validation - controlled for: age, duration of use, calendar year (as a proxy for BMI)
2011	Israel	n=329,995 ~820,000 ♀-yrs f/u 1,017 events[24]	-compared to 3rd gen. CHCs, use of DRSP had an ↑risk of VTE, RR 1.43 ($CI_{95\%}$ 1.15-1.78) -compared to 2nd gen. CHCs, use of DRSP had an ↑risk of VTE, RR 1.65 ($CI_{95\%}$ 1.02-2.65)	-independent, historical cohort study -use of DRSP was not associated with ↑ risk of arterial thrombotic events(TIA or CVA)

Pub Yr = publication year; **Rx** = prescription; **RR** = relative risk; **$CI_{95\%}$** = 95% confidence interval; **PE** = pulmonary embolism; **2nd & 3rd gen CHCs** = second & third generation combined hormonal contraceptives; **TIA** = transient ischemic attack; **CVA** = cerebral vascular accident; **LNG** = levonorgestrel **f/u** = follow-up; **mo** = month; **avg** = average; **HR** = hazard ratio; **BMI** = body mass index; ♀ = woman; **OR** = odds ratio; **2˚** = secondary

What are some other potential safety concerns related to DRSP use?

- Specific to DRSP is the *theoretical risk* of hyperkalemia in high-risk patients. This has lead to warning labels indicating that DRSP containing CHCs should not be used in women with renal, hepatic or adrenal insufficiency. When used in combination with other medications that may ↑K^+ (e.g. ACEi, ARB, NSAID), serum levels should be checked during the first treatment cycle. Several studies have suggested that DRSP containing CHCs are no more likely than other CHCs to cause this adverse effect.[12,13]

Appendix

Table 4: Risk factors for VTE [14,15]
advancing age
previous VTE
pregnancy & postpartum
obesity (BMI ≥ 30)
recent surgery, especially in the past 3 months
major trauma
immobility (e.g. bed rest)
cancer
venous compression (e.g. tumor)
myeloproliferative disease
acute medical illness
current hospitalization
noninfectious inflammatory conditions (e.g. nephrotic syndrome)
central venous catheterization
inherited or acquired hypercoagulable states
long distance travel, by air or land

Table 5: Therapies that may increase the risk of VTE [14,15]
combination hormonal contraceptives (CHCs)
hormone replacement therapy, especially estrogens
selective estrogen receptor modulators, eg. tamoxifen, raloxifene
erythropoiesis-stimulating agents
cancer therapies (hormonal, chemo, or radiation) e.g. sunitinib, cisplatin, thalidomide
? atypical antipsychotics [16]

Comments:
- debate exists over **smoking** as a risk factor for VTE[17-19]
- MEGA study[17]: smoking appears to synergistically ↑ the risk of VTE in CHC users; ♀ who use CHCs and smoke have an 8.8 fold increased risk compared to never smokers not using CHCs
- greatest risk of CHC-associated VTE may occur during the **1st year of use**

References on page 3 (available online at www.rxfiles.ca)

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Extras

www.RxFiles.ca

Regarding the 2011 Danish study; additional data (See table above for limitations of trial data)

A. The Danish national cohort study[24] published in 2011 (Lidegaard) showed that relative to levonorgesterol (2nd gen), the adjusted rate ratios (age, duration of use, calendar year (proxy for BMI), education) (95% CI) of the VTE risk with desogestrel (Marvelon) was 2.24 (1.65-2.95), drospirenone (Yasmin) was 2.09 (1.55-2.82) and cyproterone (Diane-35) was 2.11 (1.65-3.02). **Actual risks:** non-users (3.7/10,000), 2nd gen (7.5-8.4/10,000), Yasmin (9.3/10,000), Yaz (10/10,000).

B. Studies to date have examined DRSP products containing 0.03 mg of ethinyl estradiol (no studies used 0.02 mg dose as a comparator in large enough numbers of women). As such, it is unknown at this time whether the reported VTE risk applies to all DRSP-containing products.[5]

"The existing evidence continues to suggest that the risk of VTE attributable to CHCs is a class effect, primarily dependent on the dose of estrogen. The perpetuation of the debate about the existence or non-existence of small differences in risk attributed to individual progestins will not lead to a consensus among the scientific community as long as the discussion is based on observational results." [20] *J Dinger (2009)*

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Other Resources Used

FDA May/11 is investigating a possible link between venous thromboembolism and drospirenone-containing contraceptives.

FDA Apr/12 has completed its review of recent observational (epidemiologic) studies regarding the risk of blood clots in women taking drospirenone-containing birth control pills.Based on this review, FDA has concluded that drospirenone-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills. Report that some epidemiologic studies reported as high as a three-fold increase in the risk of blood clots for drospirenone-containing products when compared to products containing levonorgestrel or some other progestins, whereas other epidemiological studies found no additional risk of blood clots with drospirenone-containing products.

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Health Canada June/11 is currently reviewing two new studies recently published in the British Medical Journal that suggest the risk of blood clots with drospirenone-containing birth control pills may be two to three times greater than with birth control pills containing another type of progestin (levonorgestrel). http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_74-eng.php

Health Canada Dec/11 has completed a safety review of drospirenone-containing oral contraceptives (marketed under the brand names Yasmin and Yaz) with respect to the risk of blood clots (venous thromboembolism, or VTE). The review determined that **drospirenone-containing birth** control pills may be associated with a risk of blood clots that is **1.5 to 3 times higher than other birth control pills**.

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