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POSITION STATEMENT

Hormonal Contraception and Risk of Venous Thromboembolism (VTE)

Introduction

In addition to providing highly effective contraception, combined oral contraceptives (COCs) afford a broad range of additional non-contraceptive benefits including regulation of menstruation with reduced bleeding and pain, improved complexion, reduction in benign breast disease, reduced ovarian cyst formation, and a 50% decrease in rates of ovarian and uterine cancer. The low doses of hormones employed in today's contraceptives are generally well tolerated and the benefit /risk balance for most women is positive.

Venous thromboembolism (VTE) remains a rare but serious complication in women who use hormonal contraception. A number of factors have been identified which increase the risk of having a blood clot in the veins of the legs or pelvis: advancing age, major surgery, immobility, obesity, cigarette smoking, a personal or family history for VTE, inherited disorders of blood clotting [thrombophilias] and pregnancy.

The best evidence available indicates that in women of reproductive age, 4-5/10,000 will have a VTE each year. Women on hormonal contraceptives have been found to experience VTE at twice this rate or around 8-9/10,000 women per year (Heinemann and Dinger 2007). To keep the risks of VTE for pill users in perspective, it is important to remember that the risk of a VTE in pregnancy may reach 29/10,000 (Heit 2005) and in the peripartum period has been reported to be as high as 300-400/10,000 (Ros HS 2001, Pomp 2008). As one of the most widely used and effective contraceptive methods, the pill reduces rates of unplanned pregnancies and actually decreases the overall rate of VTE in the population in comparison to populations without access to effective contraception (Ory 1983). When identified and treated appropriately with anticoagulation, most cases of VTE resolve. However, in some cases, the clot dislodges and travels to the lungs (pulmonary embolism) with 1/100 cases having a fatal outcome. This means the death rate due to oral contraceptive use is <1/100,000 women per year – similar to the risk of death from other uncommon causes (e.g. falls, drowning, poisoning, domestic violence) and much lower than the risk associated with pregnancy (8/100,000).

Controversy continues about whether certain hormonal contraceptives may have a lower risk of VTE than others and sporadic media reports of deaths associated with certain new contraceptive methods has generated worry and confusion among contraceptive users as well as contraceptive providers.

The SOGC regularly reviews the scientific literature that addresses the risks of VTE with different contraceptive methods and provides this update as of February 2013.

The Evidence

The ideal study to address the risk of VTE with a new contraceptive method would compare VTE rates in similar women (similar age, weight, etc.), with similar risk factors (smoking, obesity, family history, etc.), initiating hormonal contraception for the first time (longer term users have lower risks than women starting contraception) with active follow-up (regular phone calls to identify any possible events) and finally, with validation of any possible events (by reviewing the actual medical record). Normally this type of high quality information is only available when the study is planned in advance to address all these concerns in prospective fashion.

As a precondition for market approval of the drospirenone-containing oral contraceptive Yasmin®, such a study was designed and conducted in Europe – the European active surveillance (Euras) Study. Initial results were reported in 2007 and showed no significant differences between the VTE risk of oral contraceptives containing drospirenone compared to those with second (levonorgestrel) or third generation progestins (gestodene, desogestrel and norgestimate) (Dinger 2007). An extension of this study out to 10 years of follow-up (LASS Study) confirmed the absence of any significant risk difference between marketed brands (Dinger 2010a).

Another well-designed prospective trial involving large European and American cohorts (the INAS study (Dinger 2010b)) is ongoing. Interim results from this trial, reported in 2012, revealed no difference in VTE risk with two drospirenone-containing products (Yaz® and Yasmin®) compared to other marketed oral contraceptives.

The Ingenix trial (Seeger 2007) was a further prospective study in the USA approved by the FDA as a precondition of market approval of Yasmin®. In this trial, first time oral contraceptive users, closely matched for risk factors, were followed prospectively to compare VTE risk with different oral contraceptives. This study found no difference in VTE risk between drospirenone-containing oral contraceptives and other marketed oral contraceptives.

In addition, a German case-control study (Dinger 2010c) using cases and controls from a primary care setting to reduce selection bias failed to find any differences in VTE risk between drospirenone-containing oral contraceptives and other marketed brands.

Together, these studies provide reassurance that drospirenone-containing oral contraceptives as well as other generation combined oral contraceptives (COCs) have similar safety profiles to that of levonorgestrel-containing COCs. They also established that the risk for VTE is highest in the first months of COC use with a fall toward baseline thereafter. It is noteworthy that a break of more than four weeks is associated with a higher risk of VTE when COCs are resumed but a switch of pills at less than a four-week interval does not impact VTE risk (Dinger 2010a).

In distinction, a number of other publications have reported a slightly greater risk of VTE with oral contraceptives containing third (desogestrel, gestodene) and fourth (drospirenone) generation progestins when compared to COCs containing levonorgestrel.

All of these publications have been retrospective – relying on data collected previously to find necessary information on VTE risk factors among cases and controls. The significant limitations of retrospective database studies are well known and have recently been reviewed. (Dinger 2009, Grimes 2010, Dinger and Shapiro 2011)

Unfortunately, when databases are developed for reasons other than research, or the data was collected for other purposes, important pieces of information are often unavailable. In most of these trials, critical information on risk factors (such as family history, obesity, etc.) is not available and could therefore not be included in the analysis. Duration of use among women in the comparison groups was often different and medical records were either not available or not used to validate presumptive diagnoses of VTE.

Other factors such as “confounding by indication” may account for differences in risk. Drospirenone-containing COCs are often prescribed for their anti-androgenic effects. Obesity and hyperandrogenemia figure prominently in the phenotype of women with polycystic ovary syndrome (PCOS) and both obesity and PCOS have been linked to increased risk for VTE (Okoroh 2012, Bird 2012). It is likely that the discrepancy between the finding of an increased VTE risk in these studies and the lack of an increased risk in the well-designed prospective studies listed above is the result of residual bias and confounding.

Perhaps the most notable database study was that of Lidegaard et al. (2009) which used data from the Danish national registry for medicinal products (established in 1994) coupled with a second registry containing hospital discharge diagnoses to determine the relationship between specific COCs and VTE risk. A total of 2045 VTE events were identified among 3.3 million women years of COC usage between 1995 and 2005. The original findings were criticised for many of the reasons outlined above and the European Medicines Agency requested a reanalysis of the data with efforts to control for certain deficiencies in the earlier report. Lidegaard et al. (2012) published an update with an attempt to control for the disputed issues (e.g. incorporating anticoagulant use for four weeks or longer as a surrogate measure to establish validity of VTE diagnosis). The subsequent publication failed to provide the comparison requested by the Reanalysis steering committee between new users of levonorgestrel- and new users of drospirenone-containing products – which when final results had previously been presented to the steering committee had demonstrated a relative risk of 1.0 indicating no increased risk (Dinger and Shapiro 2011). This and other criticisms about the validity of the original data have cast doubts on the study’s conclusions.

The Dutch Mega Study (Van Hylckama Vlieg 2009) was designed to evaluate environmental and genetic factors influencing VTE. The authors performed a retrospective case control study to examine the effects of different oral contraceptives (OCs) on VTE. Controls were found in an unusual way with many being partners of men who were seen in thrombosis clinics and the remainder being found through random digit dialing. Despite the authors’ conclusions about differential VTE risks between various COCs, their data showed hazard ratios for various OCs with wide and overlapping 95% confidence intervals indicating no statistically significant differences for drospirenone- and levonorgestrel-containing COCs.

Two case control studies (Jick et al 2011, Parkin et al 2011), based on the US Boston Collaborative and the UK General Practice Research Database reported odds ratio for VTE with drospirenone versus levonorgestrel COCs as 2.3 and 2.9 respectively, but have been criticized for many of the shortcomings known to confound the result in retrospective database studies (Heinemann and Heinemann 2011).

A database study from Israel (Gronich et al 2011) found a non-significant increase in risk for VTE with drospirenone versus levonorgestrel COCs (relative risk 1.52 CI 0.94-2.46) when the analysis was restricted to first time users. In addition, no validation of diagnoses was conducted by review of medical records in this analysis.

Finally, the FDA conducted its own study (Sidney 2013) utilizing data from two large health care databases (Medicaid and Kaiser Permanente). They reported an increased VTE risk with drospirenone-containing COCs (hazard ratio 1.77, CI 1.33-2.35). The authors acknowledge that information was missing on important covariates (obesity, personal and family history of thrombosis, lifetime use of hormonal contraceptives and smoking) and that the comparator group had COCs with varying estrogen dosages. The FDA study group is planning further research to attempt to better clarify these issues.

Conclusions:

In reaching conclusions about the relative VTE risk of third and fourth generation COCs compared to COCs with levonorgestrel, it is important to examine the strength of the evidence. The highest quality studies are those prospectively designed for the express purpose of evaluating VTE risk. Information on critical risk factors is collected prospectively, participants are followed carefully to minimize 'lost-to-follow-up', to ensure that the prescribed medication has been taken and to identify possible adverse outcomes. Finally all outcomes are evaluated to confirm or refute a diagnosis of VTE by examination of the medical record. These studies have not shown any significant differences in VTE risk among marketed COCs.

Jensen and Trussel (Contraception 2013, in press) have summarized the issue well in a recent editorial:

“Prospective cohort studies provide the highest quality of evidence on uncommon and rare side effects associated with hormonal contraception. The results of database studies can be useful when no better data are available, but should be weighted below those of well-designed and sufficiently powered prospective studies. These prospective studies effectively trump the results of database studies.”

The risk of VTE with any COC is increased over that of a non-pregnant non-COC user but is considerably lower than the risk of VTE in pregnancy and the postpartum period. Overall, the risk of VTE in COC users is very low and, for most women, the benefits of this effective form of contraception will outweigh the risks (Raymond 2012). Fear and confusion resulting from media coverage of rare events (death from COC induced VTE of <1/100,000) has the potential to create far greater harm as inadvertent pregnancies are generally the result of panic stopping of COCs and these pregnancies themselves carry greater risks for VTE. Such adverse effects on public health have been documented in a number of countries following pill scares in the past (Reid 2011).

Recommendations:

- 1) The risk of VTE in COC users is very low and for the majority of women the benefits of COCs outweigh the risks.
- 2) Health-care providers should assess risk factors for VTE as one component of identifying the optimal choice of contraception for a given woman.
- 3) Health-care providers should understand that the risk of VTE in COC users is highest in the first months of use, falling towards baseline thereafter. Pill breaks should be discouraged as there is no evidence of benefit and breaks of one or more treatment cycles may reintroduce the elevated risk that occurs when COCs are initiated.
- 4) Women should be counselled about the risk of VTE with any estrogen-containing hormonal contraceptive and should be advised about signs and symptoms and what to do if these occur. To maintain perspective, it is useful to explain that the risk of VTE in pregnancy and the postpartum period is much higher than with COC use.
- 5) Women using COCs should be advised that the highest quality evidence available at this time does not suggest a difference in VTE risk based on the type of progestin in the COC.

References:

- Heinemann LAJ, Dinger JC. Range of published estimates of venous thromboembolism incidence in young women. *Contraception* 2007; 75:328-336
- Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med* 2005; 143(10):697-706
- Ros HS, Lichtenstein P, Belloc R, Petersson G, Cnattingius S. Increased risks of circulatory diseases in late pregnancy and puerperium. *Epidemiology* 2001; 12:456–460
- Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJM. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. *J Thromb Haemost* 2008b; 6: 632–637
- Ory HW. Mortality associated with fertility and fertility control: 1983. *Family Planning Perspectives* 1983; 15:57-63
- Dinger JC et al. The safety of a drospirenone-containing oral contraceptive: final results from the EURAS on OCs. *Contraception* 2007;75:344-354
- Seeger JD et al. Risk of thromboembolism in women taking EE/DRSP and other oral contraceptives. *Obstet Gynecol* 2007; 110:587-593
- 2010a Dinger J, Do Minh T, Moehner S. The risk of venous thromboembolism in OC users: time patterns after initiation of treatment. *Pharmacoepidemiol Drug Saf* 2010; 19: S214–5 (abstract presented at the 26th ICPE, 19–22 August 2010).
- 2010b Dinger J, Bardenheuer K, Moehner S. The risk of venous thromboembolism in users of a drospirenone-containing oral contraceptive with a 24-day regimen – results from the INAS-OC study. *Fertil Steril* 2010; 94(4 [Suppl.]): S3
- 2010c Dinger J, Assmann A, Möhner S, et al. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. *J Fam Plann Reprod Health Care* 2010; 36(3): 123–9
- Dinger J. Oral contraceptives and venous thromboembolism: old questions revisited. *J Fam Plann Reprod Health Care* 2009; 35(4):211-213
- Dinger J, Shapiro S. Combined oral contraceptives, venous thromboembolism, and the problem of interpreting large but incomplete datasets. *Fam Plann Reprod Health Care* (2011).
- Grimes DA. Epidemiologic research using administrative databases. Garbage in Garbage out. *Obstet Gynecol* 2010;116(5):1018-1019
- Okoroh EM, Hooper C, Atrash HK, Yusuf HR, Boulet SL. Is polycystic ovary syndrome another risk factor for venous thromboembolism? United States 2003-2008. *Am J Obstet Gynecol* 2012;207:377.e1-8.
- Bird ST, Hartzema AG, Brophy JM, Etminan M, Delaney JAC. Risk of venous thromboembolism in women with polycystic ovary syndrome: a population based matched cohort analysis. *CMAJ* 2012; DOI:10.1503
- Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 2009; 339: b2890.

Lidegaard Ø, Nielson LH, Skovlund CW, *et al.* Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001–10. *BMJ* 2012;344:e2990

Van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. Effects of oestrogen dose and progestogen type on venous thrombotic risk associated with oral contraceptives: results of the MEGA case-control study. *BMJ* 2009; 339: b2921

Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *BMJ* 2011;342:d2151.

Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested casecontrol study based on UK General Practice Research Database. *BMJ* 2011;342:d2139.

Shapiro S, Dinger J. Risk of venous thromboembolism among users of oral contraceptives :a review of two recently published studies. *J Fam Plann Reprod Health Care* 2010; 36: 33–8.

Heinemann K, Heinemann LAJ. Comparative risks of venous thromboembolism among users of oral contraceptives containing drospirenone and levonorgestrel. *J Fam Plann Reprod Health Care* 2011; 37(3):132-5

Gronich N, Lavi I, Rennert G. Higher risk of venous thrombosis associated with drospirenone-containing oral contraceptives: a population-based cohort study. *CMAJ* 2011; 183(18):E1319-25

Sidney S, Cheetham TC, Connell FA, Ouellet-Hellstrom R, Graham DJ, Davis D, Sorel M, Quesenberry CP Jr, Cooper WO. Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users. *Contraception* 2013;87:93-100

Jensen JT, Trussell J. Communicating Risk: does scientific debate compromise safety? *Contraception* 2012; *Contraception* 86 (2012) 327–329

Raymond EG, Burke AE, Espey E. Combined hormonal contraceptives and venous thromboembolism: Putting the risks into perspective. *Obstet Gynecol* 2012; 119(5): 1039-1044

Reid RL. Oral Contraceptives and Venous Thromboembolism: Pill Scares and Public Health. *JOGC* 2011; 33(11):1150-1155