CORRESPONDENCE

Hormonal Contraception—What Kind, When, and for Whom?

by Prof. Dr med. Inka Wiegratz, Prof. Dr med. Christian Thaler
in issue 28-29/2011

Side Effects

I read the article on hormonal contraception with great interest. The summary is easy to understand and has clarified some issues for me while serving as a refresher regarding others. However, I had been hoping that the authors would have also written about the following questions that are of major importance in routine general medical practice: depression triggered by the pill, increased appetite owing to the pill, edema resulting from the pill, increase in breast size because of the pill, sometimes including stretchmark formation prompted by the pill, and pill-induced changes to a woman's libido. It is worth mentioning that every packet of contraceptive pills includes information about the consequences of missing a pill, and what to do in such a scenario.

DOI: 10.3238/arztebl.2011.0768a

REFERENCES

1. Wiegratz I, Thaler CJ: Hormonal contraception: what kind, when, and for whom? Dtsch Arztebl Int 2011; 108(28-29): 495–506.

Hubertus Tesdorpf
Bad Oldesloe
h.tesdorpf@googlemail.com

Conflict of interest statement
The author has received honoraria for presentations from Mundipharma.

Risk of Venous Thromboembolism

Wiegratz and Thaler provide a comprehensive overview of hormonal contraception using the combined oral contraceptive (COC) pill, while also discussing side effects and risks (1). Unfortunately the risks are not comprehensively discussed, and the current state of knowledge is not reflected. With regard to the risk of venous thromboembolism, this may be because of the timing of the article submission.

The authors explain that there are indications of a modified risk for venous thromboembolism as a result of the gestagen component, and that combined preparations including desogestrel, gestodene, and cyproterone acetate entail a higher risk than COCs that include levonorgestrel. This statement is correct, but the authors make no mention at all of the more recent data concerning the risk of venous thromboembolism when using COCs containing drospirenone (2, 3). This is inexplicable since drospirenone-containing COCs are among the most commonly prescribed hormonal contraceptives in Germany (4) and the European Medicines Agency (EMA) has looked into assessing the risk for venous thromboembolism in association with several COCs on the basis of more recent study results as early as in March 2010 and, most recently, in May 2011 (see www.ema.europa, plenary meeting, March 2010 and May 2010).

The EMA classes the risk for COCs containing drospirenone as higher than for COCs containing levonorgestrel, and it assumes that it corresponds to the risk associated with COCs containing desogestrel and gestodene.

In a notice in this issue of *Deutsches Ärzteblatt* (in German), the risk of venous thromboembolism is the subject of further discussion, as in our opinion the EMA's assessment should be considered in the individual prescription of any COC.

DOI: 10.3238/arztebl.2011.0768b

REFERENCES

1. Wiegratz I, Thaler CJ: Hormonal contraception: what kind, when, and for whom? Dtsch Arztebl Int 2011; 108(28–29): 495–506.
2. 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.
3. Parkin L, Sharples K, Hernandez RK, Jick SS: Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. BMJ 2011; 342: d2139.
4. Schwabe U, Paffrath D (eds.): Arzneiverordnungs-Report 2010. Berlin, Heidelberg: Springer Medizin Verlag, 2010.

Prof. Dr. med. Ursula Gundert-Remy
Dr. med. Thomas Stammschulte
Geschäftsstelle der Arzneimittelkommission
der deutschen Ärzteschaft Berlin
Thomas.Stammschulte@akdae.de

Conflict of interest statement
The authors declare that no conflict of interest exists.

Alternatives

The authors deserve thanks for their accomplished summary of such a complex topic (1); however, we wish to make some additional comments from a specialist perspective.

Although the title of the article promises a comprehensive overview of all hormonal contraceptive methods, it actually discusses merely combined preparations, and the main emphasis is on the contraceptive pill. The reason given—that all other methods were of lesser importance in Germany—may well be correct, but is a disappointment for readers expecting a comprehensive overview and thus satisfactory comparability. What was not mentioned at all was the trend found among many women, not to want to ingest any more

hormones and to look for genuine alternatives—which are actually available, and even as high-quality products.

At least the gestagen methods, which are effective in the long term, are clearly superior to the pill in terms of the Pearl index, in particular because of the reduced potential for missing a dose. Breakthrough bleeding—a common side effect in the initial phase—can be corrected by selecting suitable patients and providing careful explanations; the success is ultimately measured on the basis of the amenorrhea that is achieved in the long term, usually without problems. When discussing the risks, the main issue is the fact that such preparations are estrogen-free (which is naturally the case for all gestagen methods) or that estrogen is reduced: In women who wish to maintain a regular monthly cycle, the dates at which they are exposed to hormones need to be borne in mind, which as the "area under the curve" (AUC) for ethinylestradiol show notable differences when the complete cycle is considered (2). It is not least on this background that parenteral and primarily vaginal access via the contraceptive ring deserves far more attention.

Newer methods, which furthermore are superior to the established ones, are essential to any discussion; individualized treatment and risk minimization are the crucial steps towards greater satisfaction and health on the women's part.

DOI: 10.3238/arztebl.2011.0768c

REFERENCES

1. Wiegratz I, Thaler CJ: Hormonal contraception: what kind, when, and for whom? Dtsch Arztebl Int 2011; 108(28–29): 495–506.
2. Van den Heuwel MW, et al.: Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. Contraception 2005; 72: 168–174.

Dr. med. Ludwig N. Baumgartner
Privatpraxis für Frauenheilkunde, München-Flughafen
baumgartner@airportgyn.de

Conflict of interest statement
Dr Baumgartner has received honoraria for acting as an adviser from MSD. He has received participation fees for conferences/continuing medical educational events, and travel and hotel expenses, from Bayer, Jenapharm, MSD, and Pfizer. Furthermore he has received honoraria for presentations from Bayer, Jenapharm, MSD, and Rottapharm-Madaus.

Serious Concerns

The detailed article on the subject of contraception provided a whole range of important details (1). It therefore is even more striking that the so-called third generation gestagen—drospirenone—is not mentioned with even a single word.

Two recent industry-independent studies (2) have reported a doubling or tripling in the tendency to develop venous thromboembolism compared with the much cheaper levonorgestrel preparations. The *Arzneitelegramm* has raised this suspicion in numerous articles and for many years (3)—and the same is true for the *Arzneimittelbrief* (4). The lay press has also taken an interest in the topic for quite some time (for example, *Spiegel*, *Süddeutsche Zeitung*), and many accusations have been brought against Bayer—the US Food and Drug Administration has reported excess mortality in women taking drospirenone-containing contraceptives.

All this may not be proof (although I do ask myself what more is actually required …), but I think it is neigh-on scandalous that this article does not even report and reflect on these serious concerns. Might there be a connection with the mentioned potential competing interests?

DOI: 10.3238/arztebl.2011.0769a

REFERENCES

1. Wiegratz I, Thaler CJ: Hormonal contraception: what kind, when, and for whom? Dtsch Arztebl Int 2011; 108(28–29): 495–506.
2. Parkin L, Sharples K, Hernandez R, Jick S: Risk of venous thromboembolism in users of oral cortraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice. BMJ 2011; 342: d2139.
3. N. N.: Nebenwirkungen – Neues zu Thromboembolien unter Drospirenon-Pillen (in Yasmin u. a.): a-t 2011; 42: 48.
4. N. N.: Häufigkeit zu Thromboembolien unter oraler Kontrazeptiva mit unterschiedlichen Gestagenen. AMB 2009; 43: 87.

Dr. med. Joachim Pries
Gemeinschaftspraxis für Allgemeinmedizin, Korbach
joachim.pries@staff.uni-marburg.de

Conflict of interest statement
The author declares that no conflict of interest exists.

In Reply:

Spontaneous occurrence of thrombosis is rare in young individuals. The risk increases with age and in women not taking hormone preparations is 2 per 10 000 per year in the 15–19 year age group and 7/10 000/y among those aged 45–49 years (1). Taking ethinylestradiol (EE)-containing combined oral contraceptives (COCs) of all generations undoubtedly increases the baseline risk. The risk increase depends primarily on the dosage of the EE component, but also that of the progestogen component. With regard to the influence of the combination of estradiol valerate and dienogest on the risk of thrombosis, data are so far lacking; for this reason this preparation was omitted from the following discussion.

Important desired and undesired effects of any COC depend on the estrogen dosage. Compared with preparations containing 30–35 µg EE, the thrombosis risk is 40% lower for a dosage of 20 µg and 60% higher for a dosage of 50 µg (2). In spite of this, combinations containing 30 µg EE remain the medication of choice for many women, including very young women, because of the poorer cycle control with 20 µg EE preparations. In view of the dose-dependent procoagulatory effects of EE, patients with a raised risk of thrombosis should be prescribed a gestagen mono-preparation.

According to what is currently known, progestogen only therapy probably does not affect the risk of thrombosis (1). However, progestogens may modify the EE-induced increase in the thrombosis risk. Many studies have shown that differences exist for the different

progestogens. COCs containing levonorgestrel (LNG), for example, double the baseline risk. Compared with EE/LNG combinations, the risk for combinations containing gestodene (GSD), desogestrel (DSG), and cyproterone acetate may be raised by up to 80%. Study results are contradictory regarding combinations containing drospirenone (DRSP); this is the reason why we did not explicitly include DRSP in our article (3, 4, 5, 6). Although it is indisputable that the absolute risk is low for all COCs, COCs are contraindicated in patients with relevant increases in the individual thrombosis risk—independently of the progestogen component involved.

Gundert-Remy and Stammschulte cite a report from the European Medicines Agency (EMA), which categorizes the risk for DRSP preparations as higher than that for LNG preparations, and compared with GSD- or DSG-combinations, the risk is reportedly similar (exact wording: "… may be similar"). Furthermore the EMA explicitly points out that the absolute risk is low and that there is thus no reason to stop taking EE/DRSP combinations.

The concluding question is whether on the basis of the available data all women should be treated primarily with EE/LNG preparations. Since the progestogen LNG exerts partially androgenic effects, patients with a predisposition may develop undesirable adverse effects when taking EE/LNG preparations—such as acne or seborrhea. The combination also seems to lack benefit in women who already have symptoms of androgenization and therefore require a COC with an anti-androgenic progestogen. Women who have premenstrual dysphoric disorder (PMDD) have been found to benefit from taking EE/DRSP with a shortened hormone-free interval.

On this background of the very low incidence of venous thrombosis we think it is acceptable to prescribe, without further restrictions, the individually best tolerated COC to healthy young women without risk factors. General thrombophilia screening before prescribing COCs—of whatever generation—is not justified as its cost-benefit profile is not favorable, and no specialist professional society therefore recommends such screening.

What is far more important is to take a detailed history and undertake a thorough examination to assess risk factors before issuing the first prescription, and annual regular controls afterwards. Furthermore, all women—especially those about to be issued with their first ever prescription—should receive comprehensive information about the possible symptoms of thrombosis and pulmonary embolism, to ensure that they seek medical treatment immediately should such an event occur. Additionally, the women should be informed that the risk of thrombosis is substantially higher during the first 3–6 months of treatment than in the time afterwards. Women with relevant risk factors should not receive any COCs, not even those of the so-called second generation.

Because of space restrictions we were not able to discuss in detail the use and risks associated with progestogen only preparations, even though they are the preferred option in certain risk groups. The same is the case for individual side effects of the pill for which satisfactory epidemiological data are lacking.

DOI: 10.3238/arztebl.2011.0769b

REFERENCES

1. Lidegaard O, Lokkegaard E, Svendsen AL, Agger C: Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009; 339: b2890.
2. Lidegaard O, Edström B, Kreiner S: Oral contraceptives and venous thromboembolism: a five-year national case-control study. Contraception 2002; 65: 187–96.
3. Dinger JC, Heinemann LAJ, Kühl-Habich D: The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on oral contraceptives based on 142, 475 women-years of observation. Contraception 2007; 75: 344–54.
4. Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM: Risk of thromboembolism in women taking ethinyletradiol/drospirenone and other oral contraceptives. Obstet Gynecol 2007; 110: 587–93.
5. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Dogge CJM, Rosendaal FR: The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results from the MEGA case-control study. BMJ 2009; 339: b2921.
6. 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: 340: d2151.
7. Wiegratz I, Thaler CJ: Hormonal contraception: what kind, when, and for whom? Dtsch Arztebl Int 2011; 108(28–29): 495–506.

Prof. Dr. med. Inka Wiegratz
Klinik für Gynäkologie und Geburtshilfe
Schwerpunkt Gynäkologische Endokrinologie u. Reproduktionsmedizin
Klinikum der Johann Wolfgang Goethe Universität Frankfurt
Inka.Wiegratz@kgu.de

Prof. Dr. med. Christian Thaler
Hormon und Kinderwunschzentrum, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Klinikum der Ludwig-Maximilian-Universität München, Campus Großhadern.

Conflict of interest statement
Professor Wiegratz has received honoraria for acting as an adviser from Bayer Healthcare. She has received travel expenses and conference participation fees from Serono, Essex, and Jenapharm. She has received honoraria for scientific presentations and expert meetings from Jenapharm, Bayer Schering Pharma, Dr Kade/Besins Pharma, Essex Pharma, and Merck-Serono. She has received honoraria for conducting commissioned clinical studies as third-party funding from Jenapharm and Bayer Healthcare.
Professor Thaler has received honoraria for acting as an adviser from Wyeth, Pfizer, MSD, and Bayer Healthcare. He has received honoraria for acting as an expert consultant from MSD and Sandoz. He has received travel expenses and hotel expenses from von MSD, Wyeth, Jenapharm, Bayer Healthcare, Merck-Serono, and Ferring. He has received funding for a research project into a third-party funds account from MSD, Merck-Serono, Baxter, and Ferring.