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Letter to the Editor

The INAS-OC study

With this third epidemiological study demonstrating no difference in the risk of venous thrombosis between users of different types of hormonal contraception, Jürgen Dinger still stands virtually alone among scientists on this important issue [1]. Many exceptional aspects of this study deserve close examination to ascertain the possible explanation for the discordant results Dinger et al report as compared to that of independent researchers throughout the world:

1. Inconsistent reporting. Three out of four main estimates in Table 4 differ from the data given in the text of the result section. The authors should clarify which of the estimates are the correct estimates.
2. Undefined terms. Nowhere in the paper is it stated how they defined "a user". How long time back from the diagnosis was an exposure considered as "current use"? It is highly unusual not to define such a basic but crucial methodological point. No information is given in case of switch – and to which cohort they allocate an event close to a switch. Without knowing the time relationship between exposure and adverse outcome, and how the analysis incorporates such definitions, it is difficult to assess the validity of the results.
3. Methodological flaws. It is a general recommendation when trying to determine the effect of hormonal contraception upon venous thrombosis, to exclude from the analysis women with known risk factors, such as pregnant women, women with cancer, women with known coagulopathies, women with previous thrombosis, and women undergoing hyperstimulation fertility treatment. The study by Dinger et al., however, appears to include all such women. Similarly, the study apparently lacks an upper age limit. Astoundingly, two of the included events were in women at 65 years!
   By including postmenopausal women, who have a high risk of venous thrombosis and who seldom take hormonal contraception, as well as women with known risk factors of venous thrombosis, the authors obscure the distinction between the comparison groups. Obviously the concern is that inclusion of such women could lead to biased results by underestimating the influence of hormonal contraception and bias the results to the null and thereby contribute to the finding of no difference between the groups.
4. Failure to control for estrogen dosage. Dinger has in several comments stressed that the estrogen dose is the most important factor determining the risk with use of hormonal contraception. Therefore it is surprising that Dinger et al. did not a) indicate which dose of estrogen their different user cohorts had, and b) that they did not adjust for estrogen dose when comparing different product types. E.g. users of combined pills with levonorgestrel may have taken pills with 50, 30-40, 30 or 20 μg estrogen, while on the other hand users of $DRSP_{24d}$ had all taken 20 μg pills. Not adjusting for such differences will certainly bring biased results. Likewise $DRSP_{21d}$ may be combined with 20 or 30 μg estrogen (in Europe). If such a dose difference according to Dinger is important, why has he nowhere indicated how the distribution between these two groups of $DRSP_{21d}$ users was? The failure to control for estrogen dose when comparing DRSP pill regimens precludes any meaningful interpretation of the data.
5. Inconsistent results in starters. Dinger and Shapiro have previously argued that it is crucial to discriminate between starters, switchers and re-starters, because starters are expected to have a higher risk of venous thrombosis than switchers and re-starters. According to their new study, and in agreement with the Danish results, the comparative risk of venous thrombosis between users of combined pills with DRSP and levonorgestrel, respectively, was similar in these three groups. But the point estimates of venous thrombosis among users of $DRSP_{24d}$ and in users of levonorgestrel pills was according to Dinger et al. *lowest* among starters, which is in conflict with the higher risk of venous thrombosis during the first six months of use (Fig. 2).
6. Undefined reference group. The main comparison group (according to the authors) is non-DRSP products. The authors fail to identify the products used by the non-DRSP comparison group. It is unknown to which extent these comparators were users of 3rd generation pills such as desogestrel or gestodene, which have been demonstrated in previous studies to increase the risk of venous thrombosis to the same extent as combined pills with DRSP.
   The same problem of an undefined comparison group applies to the Ingenix study, which Dinger et al. rely upon as support for their findings. Despite the considerable financial resources provided by Bayer, the publication by

Dinger et al. lack basic methodological details, analysis transparency and incomplete reporting of results which precludes a meaningful interpretation of their results.

7. Claim of superior study design. Dinger has in several comments argued that his data is superior to other studies because it includes information on body mass index, and suggests further that missing information about body mass index in other studies may invalidate the results. Yet Dinger has previously proved, and his current data again confirms, that body mass index is not a confounding factor in the data analysis. Dinger's continued claim of the importance of adjustment for body mass index is not supported by his own analysis.

In conclusion, I recommend caution in taking the results of the new INAS study at face value. The profound critique of Danish studies included in the paper will be discussed in a separate commentary.

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Reference

[1] Dinger J, Bardenheuer K, Heinemann K. Cardiovascular and general safety of a 24-day regimen of drospirenone-containing combined oral contraceptives: final results from the International Active surveillance Study of Women Taking Oral Contraceptives. Contraception 2014. http://dx.doi.org/10.1016/j.contraception.2014.01.023.