

Comment on 'Statement on combined hormonal contraceptives containing third- or fourth-generation progestogens or cyproterone acetate, and the associated risk of thromboembolism': author's response

I would like to thank Drs Terplan and Zuckerman for their comments¹ on the recently published position statement,² which myself and the other cosignatory authors take very seriously.

If I may summarise Drs Terplan and Zuckerman's argument. It starts with the assumption that there is now clear evidence proving that levonorgestrel (LNG)- and norethisterone acetate (NETA)-containing combined oral contraceptives (COCs) have half the risk of all other combined hormonal contraceptives (oral, transdermal, transvaginal) containing four 'newer' progestogens, namely desogestrel, gestodene, drospirenone and cyproterone acetate. Following this statement Drs Terplan and Zuckerman argue that the public health conclusion has to be that the use of the newer preparations has to be limited to special indications and that the older preparations provide

health care professionals and women with enough possibilities to protect women against unwanted pregnancies. Drs Terplan and Zuckerman argue that due to the fact that millions of women take COCs it is a public health duty to establish this policy of prescription to save many women's lives, and that statements like ours are based primarily on opinion rather than scientific facts and that the authors of the statement² are very likely driven by interests related to pharmaceutical companies leading them to "hostile behaviour towards physicians who are driven by evidence and concern for women" (assuming that the authors of the statement are not interested in evidence nor have concerns for women).

My response to the points above is as follows.

1. Drs Terplan and Zuckerman assume that there is now a high level of evidence regarding the significant risk difference between older and newer progestogens and that any doubts must come from physicians with hidden agendas. There are, however, questions which currently remain unanswered, including:
 - a. Why do prospective studies find no difference?
 - b. Are registry data appropriate to answer the question about differences?
 - c. Some questions about biological plausibility. The oral progestogen-only contraceptive with a new progestogen seems not to increase venous thromboembolism (VTE) risk. The increased risk compared to LNG when both are administered in the combined form must be mediated through a difference in the impact of ethinylestradiol (EE). This difference must be pharmacologically such that it "doubles" the action of EE. This has not been shown in laboratory investigations.
 - d. How can it be explained that the vaginal ring, which provides the lowest exposure to EE in pharmacokinetic studies, nevertheless apparently has a higher risk compared to LNG-containing oral contraceptives, while the patch, which contains the progestogen with the lowest risk (norgestimate) has an even higher risk than the ring?
2. We have stated that these questions are scientifically legitimate and that we would need more well-designed prospective studies with participants stratified according to age, weight, family history and behavioural risks. I think that this statement is not based on resistance to evidence and that Drs Terplan and Zuckerman's assumption about the hidden agenda is just what is called "ideological debate" in the statement.²
2. Drs Terplan and Zuckerman amplify the stated risks to millions of users. This is in my view scientifically not correct because they amplify also the doubts and do not take into account that in different populations and races thromboembolic risks are different.
3. "Our review of all the published studies has failed to find any evidence that it is necessary to offer more than a dozen of the safer types of oral contraceptives to maximise patient satisfaction, contraceptive use or compliance." What Drs Terplan and Zuckerman are saying is that basically with two progestogens in COCs (NETA, LNG) we have enough tools to tailor contraceptives to individual needs. This is an interesting assumption that we have addressed in our statement.² We believe that this has yet to be proven and therefore we suggest what is needed are clinical studies that have as outcomes not only VTE but also unwanted pregnancies, rates of discontinuation, compliance, and long-term tolerability. Clinical experience and the statistics about unwanted pregnancies show in our opinion that there are still unmet needs among women regarding contraception, and that choices of different methods and ways of application may be really important for women and not just an invention or opinion of experts.

We fully agree that we should take any risks associated with different contraceptive methods very seriously and reduce risk as much as possible; therefore the studies that have been performed are important and the results should be communicated to

patients to help them to make informed decisions and choices.

From a public health point of view, taking into account the presently available evidence, all women should use the progestogen-only intrauterine system (IUS) as this has the highest efficacy and lowest health risk. The individual decision will, however, always have to take into account and weigh efficacy, health risks, tolerability, health benefits, route of application, preferences and values. This is why we have stressed the importance of choice in our statement.²

One final remark concerning the fact that the main author and many of the coauthors to the statement collaborate with pharmaceutical companies. I believe that there are shared objectives (providing all women with effective, safe and well-tolerated contraceptive methods) and clearly different objectives (making money from the products vs having the best methods available for our patients independent of the price). There are possible dangers: for example, companies withholding information, or physicians not being guided by the best interests of their patients. These dangers have to be detected, named and avoided. The mere fact of collaboration is however not a bias, nor a danger in itself, but is often necessary in order to make scientific and practical progress.

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REFERENCES

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- 2 Bitzer J, Cosignatories. Statement on combined hormonal contraceptives containing third- or fourth-generation progestogens or cyproterone acetate, and the associated risk of thromboembolism. *J Fam Plann Reprod Health Care* 2013;39:156–159.