

# Statement on combined hormonal contraceptives containing third- or fourth-generation progestogens or cyproterone acetate, and the associated risk of thromboembolism

Johannes Bitzer

## Cosignatories

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## A NEW PILL SCARE? HOW DID IT COME ABOUT AND HOW SHOULD WE TACKLE IT?

The controversy around the combined hormonal contraceptives (CHCs) of the so-called third (containing gestodene or desogestrel) and fourth generation (containing drospirenone, DRSP) has reached a highly emotional political dimension in which all those who are professionally responsible for women's health are involved: the national health authorities, the pharmaceutical companies, the professional organisations, the prescribers, the media and the public (i.e. the current or potential users of CHCs).

The – initially scientific – controversy has now led to a public health dispute that culminated in the decision of the French authorities to withdraw the combination containing ethinylestradiol (EE) and cyproterone acetate (CPA) from the market. The potential impact of this measure, namely the loss of confidence in *all* CHCs, could be quite serious.

## WHAT TRIGGERED THIS CRISIS?

Several registry-based studies published in the *British Medical Journal*, particularly

the one based on the Danish Registry, indicated that there is an increased risk of venous thromboembolism (VTE) associated with the intake of third- and fourth-generation combined oral contraceptives (COCs) compared to preparations containing the progestogen levonorgestrel (LNG).<sup>1–5</sup> The relative risk (RR) was around 2, and the absolute attributable risk was estimated to be (dependent on the background prevalence rate) between 2 to 8 per 10 000 users per year.<sup>6</sup>

A very recent systematic review and meta-analysis of the possible link between treatment with CHCs and VTE concluded that, in this regard, (1) CHCs containing LNG or norgestimate were the safest, (2) those containing desogestrel, DRSP or CPA were associated with a significantly higher risk than CHCs containing LNG, and (3) the augmented risk of VTE found for pills containing gestodene compared to COCs with LNG appeared to be smaller than in earlier studies.<sup>7</sup>

These results contrast with those of published prospective cohort studies, sponsored by Bayer HealthCare, at the request of the European Medicine

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Agency (EMA) and the Food and Drug Administration (FDA) for an expanded post-marketing surveillance, which did not find such differences. This discrepancy led to an intensive scientific discussion among epidemiologists about possible confounders and biases in the published studies.<sup>8,9</sup>

The authorities at that time informed women about the controversial results and the possible – but not definitively proven – increased risk of the newer preparations. They encouraged healthcare professionals to balance risks and benefits of the different preparations in a process of shared decision-making with the individual woman, and advised women to continue treatment with the currently used contraceptive to avoid the previously observed rise in the number of abortions following the ‘pill scare’ in 1995.<sup>10,11</sup>

The unresolved scientific debate continued thereafter and was given new impulse by different publications. One publication reported an increased risk of VTE in users of COCs containing DRSP and CPA.<sup>12</sup> Another one based on the Danish Registry indicated that treatment with the transdermal patch and the vaginal ring was also linked to a greater risk of VTE, whereas the LNG-releasing-intrauterine system (LNG-IUS) did not increase or even decreased that risk compared to non-users. In this publication the authors gave practical advice about how to switch from the aforementioned contraceptives to either a LNG-containing pill, a LNG-IUS or a non-hormonal method.<sup>13,14</sup> Again, these results are in direct contrast to those of another cohort study conducted in the USA, which did not show a difference in VTE risk between the vaginal ring and COCs.<sup>15</sup>

These publications warning about the increased risk of third- and fourth-generation contraceptives and CPA-containing pills were received with great interest by the media. Dramatic individual cases of VTE in women using a newer COC or a pill combining EE and CPA were changing the scientific controversy into a highly emotional debate in which the original discussion about epidemiological methods and statistics turned into a fight between ‘ideologies’.<sup>16–20</sup>

On one side are the pharmaceutical industry, epidemiologists, physicians who work with the pharmaceutical industry, scientific societies and practitioners who see the usefulness of these new contraceptive methods and want them to remain available for women. On the other side are the epidemiologists, practitioners, journalists and lawyers who feel that they must keep women from resorting to using these newer methods, which they consider to be associated with a greater risk to health.

The first group is accused by the second one of acting out of a commercial interest. The second group is blamed by the first one for seeking restrictions and a change of practice based at best on debatable evidence and at worst on biased reporting, thus creating

fears that may lead to another pill scare with the consequences that were seen previously. All of this has created a climate in which critical and considered thinking has become very difficult, and which has put so much pressure on the authorities that the latter feel compelled to act, as has happened in France recently. This crisis is to the disadvantage of all, but especially to women.

Epidemiological data – and, in particular, registry data – cannot stand alone. Only when these data are combined with the outcome of solid clinical trials is there a platform for establishing valid clinical guidelines.

## OUR PLEA: LET US COME BACK TO OUR SHARED OBJECTIVES<sup>21</sup>

1 It can be taken for granted that all parties involved in this ‘confrontation’ share the same objective, namely to achieve the best for women’s health and to put at their disposal effective and well-tolerated contraceptives.

2 Everybody concurs that contraceptive methods are needed that possess the greatest possible efficacy, safety and tolerability and, if possible, additional health benefits. All these elements should be integrated in the individual risk/benefit evaluation.

3 Everyone is probably in agreement that no method currently available or likely to be developed at a later date will be 100% effective, risk-free, well tolerated by all users, and associated with non-contraceptive benefits justifying and facilitating its long-term use.

4 In view of this fact, everyone is likely to acknowledge that a large spectrum of methods should be available in order to tailor contraceptive choice to individual women’s needs.

5 Everyone concerned undoubtedly also concedes that each contraceptive decision must be properly balanced and based on the best evidence on record about risks and benefits. This information should be delivered in a way that helps women to understand the scientific evidence and takes into account women’s needs and values so that, after having been fully informed, they are able to individually weigh up the relative importance of this evidence. By educating and counselling women in this way, they will be appropriately informed in respect of the decision-making process.<sup>22</sup>

## WHAT ARE THE CONCLUSIONS BASED ON THESE OBJECTIVES?

All parties involved must be interested in conducting well-designed prospective studies addressing the relevant outcomes of the use of contraceptive methods (efficacy, safety, side effects, non-contraceptive benefits, and so on). This will require the collaboration of health authorities, industry, epidemiologists, physicians and women’s organisations.

At the present time, data are lacking or are controversial. As a result, healthcare professionals are left with a degree of uncertainty that they will inevitably end up sharing with their patients. It is important that patients receive balanced information from their healthcare providers, which then helps them to choose the contraceptive method that best fits their individual needs and their risk profile.<sup>21,22</sup>

### SUMMARY OF THE CURRENT EVIDENCE CONCERNING THE RISK OF VTE

Several registry-based case-control studies have come to the conclusion that the use of third- and fourth-generation CHCs is associated with a higher risk (RR 1.6–2.4) of VTE than that related to the use of CHCs containing LNG. Two large cohort studies did not find such a difference.

Many factors contribute to VTE risk (e.g. age, duration of use, weight, family history, etc.), which makes epidemiological studies vulnerable to bias and confounders, and may explain contradictory results.<sup>21</sup> Additional prospective well-controlled studies are needed.

The inherent inability of database studies to adequately control for baseline confounders render this design less suitable for providing further clarification.

Some epidemiologists question whether the RR increase of around 2 described in the aforementioned case-control studies reflects a clinically relevant difference.

Several studies have shown that the risk of VTE during pregnancy and the postpartum period is considerably higher (29–300 per 10 000 users) than during use of a CHC.<sup>21</sup>

### PRACTICAL RECOMMENDATIONS

In order to reduce the VTE risk it is most important to avoid prescribing CHCs to women at elevated risk for VTE. The World Health Organization *Medical Eligibility Criteria for Contraceptive Use*<sup>23</sup> should serve as a first point of guidance for prescribers.

Women who have a higher risk of VTE due to obesity, smoking, family history of VTE or cardiovascular disease should undergo a personal risk assessment and be advised appropriately.

The hormonal contraceptive methods with the lowest VTE risk are progestogen-only contraceptives. While there is some evidence from registry studies that CHCs containing LNG are associated with less risk than those containing third- and fourth-generation progestogens, large, well-designed cohort studies have not confirmed this difference in risk, and the controversy is not yet resolved.<sup>24</sup> Even if third- and fourth-generation pills are associated with a higher RR, the absolute difference in risk is small, and is estimated by some authors to be of the order of 4–6 attributable cases per 10 000 users per year.<sup>20,24</sup>

The risk of death from VTE is low. Based on a RR of 2, the excess risk of death for a woman taking modern pills is 1 in 100 000, which is much lower than the risk of everyday activities such as cycling.<sup>22</sup>

In the decision-making process regarding the choice of a contraceptive method by the individual patient, VTE risk is but one element in the equation. Other elements are efficacy, tolerability, additional health benefits, and whether or not the patient can/will use an alternative method. These factors must be taken into account and discussed with the individual patient. Results from long-term cohort studies on the positive impact of the use of hormonal contraceptives on global health parameters of women should be part of the information given to women.<sup>25–27</sup>

Both epidemiological data and clinical trials must be taken into account when best practice is defined. Regulatory restrictions of previously registered methods should only be made after careful assessment of all the available evidence.

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