The bitter pill

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A FRENCH PILL SCARE

The opinion of Marion Larat is that "nobody, but nobody should take the third- and fourth-generation pills".[1] This view is not surprising as she suffered a devastating stroke at the age of 18 years.[2] A subsequent enquiry linked her cerebral vascular accident to Méliane®,[3] a 20 µg pill containing gestodene that she had been prescribed for contraception. In December 2012, Marion Larat successfully sued the manufacturer, Bayer, and the French drug regulatory board Agence national de sécurité du médicament et des produits de santé (ANSM) for damages. Her case was widely publicised in the media and 30 similar lawsuits soon followed.

In January 2013, the Minister for Health, Marisol Touraine, announced that France's social security system would no longer reimburse prescriptions for third- and fourth-generation pills.[4] At the time around half of the five million French women on the combined pill were taking such pills,[5] which cost more to the state than older formulations. Plans were made to strip midwives and nurses of their pill-prescribing powers.[5] The ANSM advised that third- and fourth-generation pills should never be used as first-line contraception and should only be prescribed if an older formulation had not been tolerated.[5] The ANSM then referred the matter to the European Medicines Agency (EMA) for further investigation.

THE PILL CONTROVERSY

Since the introduction of the combined oral contraceptive pill (COC) in the 1960s, an association between ethinylestradiol (EE) and venous thromboembolism (VTE) has been apparent. The amount of EE in pills has lessened over time to reduce thrombotic potential as well as estrogenic side effects. Older pills contain testosterone-derived progestogens and can have androgenic side effects. Newer formulations have been developed that contain less androgenic progestogens and so aim for better tolerability.

Progestogens have been arbitrarily categorised into 'generations' based on their chemical structure and timing of introduction onto the market. This is neither a standardised nor a scientific system, which makes interpretation of data more challenging. Numerous epidemiological studies have been published suggesting that newer-generation combined hormonal contraceptives (CHCs) have higher thrombotic potential than older formulations. It has been postulated that progestogens such as levonorgestrel (LNG) have anti-estrogenic properties that reduce prothrombotic potential when combined with EE. This effect is apparently absent with newer progestogens.[6]

However, studies have also been published that do not demonstrate increased rates of VTE with newer formulations and so cast doubt on this link. The discrepancy has led to heated scientific debate about design flaws, possible confounders and biases in the studies.[7 8] Furthermore, some experts have questioned the biological plausibility of the anti-estrogenic effect of older progestogens. Norelgestromin in the transdermal patch is metabolised to LNG yet some studies suggest that the patch is associated with higher VTE rates. Similarly users of the vaginal ring are exposed to lower doses of EE and yet appear to have higher thrombosis risk.[7]

THE EMA REPORT ON CHC

Following the French request for clarification, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) examined all available data regarding VTE risk with CHC and published a report in January 2014.[9] The overall finding was that the benefits associated with using any CHC far outweigh risks of serious adverse events in most women. VTE is fatal in only 1–2% of sufferers. All CHCs increase the risk of VTE slightly, but some products may increase it marginally more than others (Table 1). The ranges of figures do overlap considerably, which raises the question of how these estimated risks should be interpreted in practice.

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Table 1 Risk of venous thromboembolism with combined hormonal contraceptives*

Category of woman	Risk of developing VTE in a year (per 10 000 women)
Non-pregnant non-user of CHCs	2
Woman using CHCs containing levonorgestrel, norethisterone, norgestimate	5–7
Woman using CHCs containing etonogestrel, norgestromin	6–12
Woman using CHCs containing drospirenone, gestodene, desogestrel	9–12

*Adapted from the *Assessment Report for Combined Hormonal Contraceptives Containing Medicinal Products*.[9]
CHC, combined hormonal contraceptive; VTE, venous thromboembolism.

The risk of arterial thromboembolism is also slightly increased with CHC use. A large Danish study estimated a risk of around 2/10 000 women in a year.[10] The PRAC concluded there was no evidence of a difference in relative risk between products.

The PRAC emphasised the importance of risk factors in the development of thrombosis, both arterial (e.g. hypertension, smoking, cholesterol and diabetes) and venous (such as obesity, smoking and immobility). These risks should be assessed, all contraceptive options explored, and shared management plans agreed with patients. CHC users should be educated about the signs of thrombotic disease and have their risk reassessed regularly to minimise adverse events.

THE FRENCH 'DIANETTE' BAN

In the midst of the contraception controversy in France, the ANSM completed a 2-year investigation into Diane-35® and its generics. Diane-35 is co-cyprindiol, a combination of 2 mg cyproterone acetate and 35 µg EE and is marketed as Dianette (as well as Clairette®, Anocin® and Cicafem®) in the UK. Cyproterone is a derivative of 17-hydroxyprogesterone acetate and has a specific anti-androgenic effect. Co-cyprindiol has been licensed since 1987 to treat androgenic conditions such as acne, seborrhoea, hirsutism and alopecia.[11] Cyproterone has potential fetotoxic effects, specifically feminisation of male fetuses. It is not a recommended monotherapy in women of reproductive years, so is combined with EE.

In 2013, 6% of all combined pill sales in France were for co-cyprindiol.[12] The ANSM report attributed 125 cases of thrombosis and four deaths to co-cyprindiol products in the preceding 25 years in France.[12] It concluded that the risk of VTE outweighed the benefit of co-cyprindiol as an acne treatment. Furthermore, its properties as an anti-ovulant were not regarded by the ANSM as adequate to recommend its use as a contraceptive.[12] In January 2013, the French authorities banned the sale of co-cyprindiol and requested further advice from the EMA on the matter.

Accordingly, the EMA's PRAC assessed all available evidence on clinical safety and efficacy of co-cyprindiol and compiled a report. The report confirmed the known risk of VTE with co-cyprindiol and concluded that the risk appears to be 1.5–2 times higher than for CHCs containing second-generation progestogens such as LNG. The risk of co-cyprindiol was comparable with third- or fourth-generation contraceptives containing gestodene, desogestrel or drospirenone.[13] The report did highlight that intermittent regimes are more common for co-cyprindiol as its licence stipulates that treatment should be discontinued on resolution of the symptoms and restarted when the condition recurs. This pattern of use is more likely to increase the risk of VTE as studies suggest that clotting risk is higher in the initial year of CHC usage[14] or after a month of non-use (additional calculations based on Dinger *et al*.).[8]

The report found off-licence prescribing of co-cyprindiol to be widespread, with 66.7% of UK prescriptions listing contraception as the main indication. There may be financial motives for recording this in the UK, but rates were also high in Germany (61%) and France (42%) where contraception is not free of charge. Moreover, in the UK 12% of prescriptions for co-cyprindiol had a concomitant COC prescription thereby potentially doubling the dose of EE taken by these women. This percentage was higher than in Germany (5.6%) and France (2.1%). Of the global spontaneous reporting of VTE carried out for post-marketing surveillance of co-cyprindiol, only 2% of the total cases of thrombosis were taking concomitant combined contraceptives. The contraceptive efficacy of co-cyprindiol was confirmed as comparable with standard COCs but this was not recommended as the sole indication for prescription.

The PRAC concluded that the benefits of co-cyprindiol outweigh the risks for treatment of moderate to severe acne related to androgen sensitivity and of hirsutism in women of reproductive age, but that it should only be used when topical and antibiotic therapies have failed. It also commented that alternative therapies for acne may also carry risks including antibiotic resistance, teratogenicity and hepatotoxicity. Regarding alopecia, in view of the limited efficacy data, the PRAC concluded that co-cyprindiol should no longer be recommended as a therapy

In conclusion, the PRAC recommended changes to the product licensing and marketing aspects of co-cyprindiol and suggested measures to reduce the risk of thromboembolism.[13]

FULL CIRCLE IN FRANCE

In January 2014, the European Commission adopted a legally-binding decision to update product information of all CHCs throughout the European Union. All combined hormonal products are now back on the market in France, including Diane-35. Not surprisingly though, the pill scare has resulted in a change in the contraceptive landscape in France, with one in five women having switched method. Use of the

contraceptive pill has dropped by 9% and French women are now opting for less effective methods such as withdrawal or natural family planning.[15]

These events show how personal tragedy, legal decisions, and emotive media reporting can influence policy and patient choice. Scientific evidence doesn't always give absolute answers and experts don't always agree.[7] Pending lawsuits involving huge amounts of money create an environment where scientists are under pressure to present indisputable evidence. Accusations of 'conflicts of interest' are inevitable,[16] and the issue of risk associated with 'the pill' has escalated into an ideological fight. Until large-scale, well-designed trials provide valid and universally accepted conclusions, it is an issue that shows no sign of being resolved.[7]

LIFE IS BITTER

In her autobiography *La pilule est amère* (*The Bitter Pill*)[2] Marion Larat describes her slow recovery from the stroke that left her hemiplegic, aphasic and epileptic. She only learnt that the pill had contributed to the thrombosis 4 years later when a haematologist diagnosed her with factor II prothrombin mutation.[2] This genetic clotting disorder can increase the risk of thrombosis on any combined pill and potentially in pregnancy.[17] Marion Larat then began her crusade against the pharmaceutical industry and the authorities. From her book it seems that her anger was not just the result of debilitating neurological sequelae and a young life derailed. Marion Larat believed she was deceived by the medical profession who, in her opinion, both failed to counsel her about the dangers of the pill and, for a long time, failed to communicate its culpability. She continues to campaign against third- and fourth-generation pills through the Association de Victimes d'Embolie Pulmonaire et AVC (AVEP).

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