Concerning: Blondon et al. Genetic testing to identify women at risk of venous thromboembolism with contraceptive pills: evidence- or hope-based tool?

With a prevalence of 1 in 1000 women among combined oral contraceptive (COC) users, thromboembolic events are not that rare [1]. In Switzerland, over 400 women using a COC present a thrombotic event that can in some cases develop into a pulmonary embolism, with serious consequences for the patient’s health [2]. In Europe, this number is estimated to be 22 000 cases per year, with an estimated direct cost of over 200 million euros to the health system.

From a patient point of view, the dramatic consequences of a thromboembolic event, publicised widely in the media since 2011, are of importance, even though we could argue that the prevalence is low. In the century of high-throughput sequencing and genome-wide association studies, the necessity to develop a robust tool to identify women at risk, with the most updated scientific evidence and technology, is clear. It is time to embrace the promise of the genomic age.

Since 1985, newer generations of pills containing different progestins, such as norgestimate, desogestrel, gestodene, drospirenone and cyproterone acetate, have been developed to overcome adverse effects such as weight gain, acne, hair loss or growth, headache, breast tension and nausea, which can be troublesome for many women using second generation pills. The increased risk of thromboembolic events associated with these new pills is well documented and recognised. The advice to use a second generation pill or progestin-only pill to decrease the risk of thromboembolism is a safer bet and probably sensible when no other options are available. However, most COC users would benefit from the newer generation pill without having a drastically increased risk of thromboembolic events compared to the second generation pill. A tool that distinguishes women at risk and compares the risks for the different generations of pill is therefore a valuable tool for COC users.

Gene Predictis® has developed such a tool, called Pill Protect®, which has been on the Swiss market since October 2015. This tool integrates clinical information about the patient with (1) genetic information on nine relevant polymorphisms (including factor V Leiden and factor II variants) present in the population with minor allele frequencies ranging from 2 to 50%, and (2) the type of pill the patient would like to use or is using. This tool was validated in a retrospective case-control study that included 794 women using COCs who had a thromboembolic event while using the contraceptive pill and 828 control women using COCs without a history of thromboembolism. The choice of a retrospective study is obvious for ethical reasons. In addition, although a prospective study would be welcome, it would require over 1 million women to obtain enough cases and statistical power for the rarest variants (2%) based on the prevalence of thromboembolic events among pill users.

Blondon et al., who have not contacted us, emphasise several points about this tool that we want to answer:

- Blondon et al. [3] argue that our validation is based on the PILGRIM study. Part of our study population was indeed derived from the cohort described in the PILGRIM study, provided to us by Prof. Morange, especially the cases. However, a large part of the controls came from other, carefully-matched general population studies. In addition, the bias present in the PILGRIM study and mentioned by Blondon et al. was known and accounted for in our statistical analyses. The family history, as well as factor V and factor II genotyping data, could not be used as such because of the way these controls were collected. In consequence, this bias was corrected in our study.

- The positive predictive value (PPV) of 88% cited in our communications reflect the PPV of the randomised case-control study that we carried out and not the final medical results given in the medical report sent to the COC prescribers. The result of the Pill Protect® tool provides an estimated absolute risk per 10 000 women per year, according to the prevalence of a thromboembolic event in the general population for each age group, as described in the literature.

- The suboptimal methodology referred to in Blondon et al. is largely assumed by these authors, as they stated that they do not know the detailed statistical approach behind the test. Our methodology was developed in collaboration with renowned statisticians, was based on a step-wise multivariate logistic regression model selection and will be published after December 2016 for business development reasons.
Blondon et al. claim that we need an independent cohort to validate our algorithm. It is not the case, since (1) the initial algorithm behind Pill Protect® was mostly developed before validation on the case-control study and had already been validated by us on smaller cohorts, (2) the design of our validation study included random assignments of training and test sets, and (3) most importantly, the final algorithm was further tested on a smaller set of samples independently collected and gave similar performance characteristics. Naturally, we would be glad to collaborate in testing our predictors in further cohorts.

In the light of these comments, we are convinced that our study is robust and well designed. We are committed to help medical doctors to optimise patient treatment and reduce the risk of adverse effects of contraceptives, which are so important in women’s daily life.

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References

