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Reactions to awareness of activated protein C resistance carriership: a descriptive study of 270 women

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Background. Around 25 million Caucasian women are carriers of the FV Leiden mutation that causes activated protein C (APC) resistance. This is a heritable condition with a lifelong increased risk of venous thromboembolism. We performed this study to investigate women's reactions to their awareness of being APC-resistant and the consequences of this awareness.

Methods. All APC-resistant women ($n = 270$) included in a prior study on APC resistance and pregnancy ($n = 2480$) were invited by written questionnaire to describe their reactions to having APC resistance, how this had changed their lives, and how they experienced our information. Answers were obtained from 215 of the 270 women (80%).

Results. More than 94% of the APC-resistant women were satisfied with knowing themselves to be APC-resistant and pleased that they had enrolled in the study. Of the women on combined oral contraceptives (COC), 84% changed their method of contraception, but 16% continued on COC. One-third of the women reported becoming more worried or afraid of getting pregnant again as a result of their awareness of being APC-resistant. The proportion of women who sought legal abortions during a 2-year period after receiving this information was similar in both subgroups: 4.4% (12/270) vs. 4.3% (94/2210), $p = 0.9$.

Conclusions. We conclude that most APC-resistant women were pleased to learn of their APC resistance status, that there was not an increased incidence of legal abortions, but almost one-third reported being more worried or afraid of getting pregnant again.

Keywords: APC resistance; Leiden mutation; combined oral contraceptives; thrombophilia testing

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The highly prevalent, hereditary, thrombophilia coagulation factor V mutation (FV Leiden) that causes activated protein C (APC) resistance affects natural anticoagulation by impairing cleavage and inactivation of activated coagulation factors V and VIII. This brings about a lifelong pro-coagulatory state associated with a fivefold increased risk of venous thromboembolism. The prevalence of APC resistance ranges between 2% and 15% among Europeans, while in mixed (predominantly Caucasian) populations as in the USA, a 5% to 6% prevalence has been reported

(1, 2). This means that some 25 million Caucasians women are carriers of APC resistance.

Whether general screening prior to pregnancy and the prescription of combined oral contraceptives (COC) would be advantageous has been discussed (1, 3, 4). The argument in favor of general screening has been that knowledge of carriership might help women decrease the risk of thrombosis by avoiding situations that put them at risk whenever possible, including the use of COC. Speaking against general screening is the concern that an awareness of APC resistance

Table I. Responses by APC-resistant women to the question: Now that you know that you are APC-resistant . . .

	Very satisfied	Satisfied	Less satisfied	Dissatisfied	No answer
Are you satisfied with the awareness?	113 (53%)	88 (41%)	11 (5%)	3 (1%)	0
Are you pleased that you entered the study?	118 (55%)	91 (42%)	6 (3%)	0 (0%)	0
Are you satisfied with the information that you have received?	38 (18%)	96 (45%)	62 (29%)	19 (9%)	0
Are you satisfied with the interval between the test and your notification?	10 (5%)	85 (40%)	69 (32%)	49 (23%)	2
Are you pleased that you have made a contribution to research?	137 (64%)	73 (34%)	2(1%)	1(0%)	2

Number and percentages are given

might result in psychological stress, bleeding complications due to inappropriate use of anti-coagulants, unplanned pregnancies due to changed contraceptives, and the likelihood that it would not be cost-effective. In addition, women might not want to know their FV Leiden status and might suffer discrimination in the life insurance system.

We performed this study to ascertain whether APC-resistant women wanted to know about their APC resistance status, or not, and the consequences of this awareness.

Methods

Between February 1994 and June 1995, all pregnant women in Malmö were invited to participate in a large prospective study ($n = 2,480$) (5). At their first routine visit during pregnancy to one of the community or private antenatal care clinics in Malmö, the women enrolled in the study were interviewed by midwives and blood was drawn for APC-resistance testing. Blood samples were centrifuged and stored in a -70° freezer, and were analyzed no earlier than 3 months after delivery. About 1 year after the last woman gave birth and all data were set, all women included in the study were informed by letter of their APC resistance status. They were also informed of the conclusions of the study, i.e. that carriership of FV Leiden is associated with an increased risk of thrombosis, but not with increased risk of other complications such as miscarriage, preeclampsia, or intrauterine growth restriction (IUGR). Heterozygous carriers were also given the following recommendations: 1) preferably use contraceptives other than COC; 2) inform their physicians of impending surgery, pregnancy or contraceptive practices; 3) that we do not plan to institute thrombosis prophylaxis in the event of future pregnancies in the absence of other risk factors; and 4) seek medical advice on suspicion of thrombosis. If a heterozygous woman wanted to continue on COC after being so informed, she was given a prescrip-

tion. Homozygous carriers ($n = 7$) were scheduled for personal instruction. They were advised not to use COC due to the attendant very high risk of thrombosis and that postpartum thrombosis prophylaxis should be instituted for 6 weeks in future pregnancies, if no other risk factors were present. Information regarding APC resistance status was considered as experimental data and was not entered in a woman's medical record, unless we were specifically requested to do so.

Two hundred and seventy women out of the 2480 in the study were found to be APC-resistant. These women were then contacted by letter from 6 to 12 months after being given the information on APC resistance (i.e. 1.5–3 years after delivery) and were given a questionnaire focusing on their reactions to the information, and how it had affected them (see Tables I and II). Two hundred and fifteen (80%) returned the questionnaire. During a 2-year period from 1998 to 1999, it was recorded whether a woman included in the study had had an induced legal abortion at Malmö University Hospital. The study was approved by the Ethics Committee of Lund University.

Table II. Answers by 215 APC-resistant women to the question: How has the knowledge of APC resistance affected you? Please mark the statements that you are in agreement with

	Yes (<i>n</i>)	%
I have stopped using combined oral contraceptives*	103	48
I will continue to use combined oral contraceptives*	19	9
I have become more worried	57	27
I think the knowledge might be advantageous in case of future surgery or an accident	188	87
I live the same way I have before	148	69
I am afraid of getting pregnant again	22	10
The information has been clear and distinct	72	33
It has been difficult for me to reach a responsible person for more information	4	7
The knowledge has been of use in the choice of a contraceptive method	101	47

*The percentages of those answering the question were 84% and 16%, respectively

Student's *t*-test was used for the analysis of continuous variables, and the χ^2 -test for categorical variables. All calculations were performed with SPSS software (Statistical Package for the Social Sciences, SPSS Inc, Chicago, USA) and *p*-values <0.05 were considered statistically significant.

Results

The mean age of women was 29.1 ± 4.8 years, maternal weight 65.1 ± 10.5 kg, and the proportion nulliparae and smokers were 47% and 18%, respectively. Most women were pleased with having been informed of their APC resistance, with having been enrolled in the study, and with the fact that they were contributing to research (Table I). More than half of the women, however, were dissatisfied with the interval between the test and the notifications, and 38% were not entirely satisfied with the information they had received (Table I). Nineteen women out of 122 (16%) answered that they had continued with COC, while 84% reported that they had stopped using COC (Table II). Regarding the questions intended to elucidate psychological stress, 27% reported that they had become more worried, 10% that they were afraid of getting pregnant again, 84% that their awareness of APC resistance might be an advantage in the event of future operations or accidents, while 69% reported that their lives were unaffected by the information (Table II). The 101 women (47%) who reported that the knowledge of APC resistance had been of use in the choice of contraceptive method were younger than those who did not answer in the affirmative (28.0 vs. 30.1, $p = 0.01$). In addition, 67 of the 103 who stopped using COC answered that the awareness of APC resistance had been of use in the choice of contraceptive method, as compared to three of the 19 who continued using COC ($p < 0.001$). In the subgroup ($n = 19$) of women who continued with COC, eight (42%) reported that they were more worried ($n = 7$), or that they were afraid of becoming pregnant again ($n = 4$). Although not included in our questionnaire and not documented, several women reported spontaneously that they had changed to a more active lifestyle and a healthier diet.

We found 4.4% (12/270) of the carriers of FV Leiden to have had at least one induced legal abortion during the 2-year period after being aware of their carriership of FV Leiden, as compared to 4.3% ($n = 94/2210$) among noncarriers ($p = 0.9$).

Discussion

Our study clearly demonstrates that most APC-resistant women prefer to know of their APC

resistance status, and that 84% of the affected women using COC found to be APC-resistant elected to stop using COC in order to reduce their risk of thrombosis. The evident dissatisfaction regarding the interval between the testing and the reply was due mainly to the design of the study. Those who were included early in the series had to wait a long time before receiving an answer and some had become pregnant again before the time of their notification. In the case of APC resistance testing in clinical practice, it should be possible to reduce the interval.

The finding that more than one-third of the APC-resistant women were not satisfied with our information could be interpreted in two ways. Either the information we gave was inadequate, or they would have liked to have known more about APC resistance. Our questionnaire was not designed with sufficient specificity to clarify this issue. However, our reason for conducting the prospective study was to increase the knowledge of APC resistance during pregnancy. We chose to supply only written information to all heterozygous carriers and personal information to all homozygous carriers to simulate a possible future situation with APC resistance screening. We were not surprised that 16% of the women on COC chose to continue taking COC. However, it was noticeable that these women ran an increased risk of becoming more worried or afraid of getting pregnant again. Few women used the opportunity to call our direct telephone number for additional information. Therefore, we were surprised that 14 women reported difficulties in contacting us for further information. One drawback of our questionnaire was that it has not been validated, especially regarding the questions on emotional stress. However, we do believe it is of importance to get the patients' perspective on thrombophilia testing.

We made a distinction between the information to heterozygous carriers, which was 'to preferably use contraceptives other than combined COC', as compared to the recommendation to homozygous carriers 'not to use combined COC'. The risk of thrombosis for 10 years of COC use, which is the mean period for users, is roughly 1% among heterozygous carriers (4) and 15% for homozygous carriers [i.e. $1/15\,000$ (incidence in background noncarriers) $\times 10$ (years of use) $\times 3$ (increased risk of COC use) $\times 5$ (increased risk of heterozygous APC resistance or 80-fold for homozygous APC resistance)]. We felt that, in the absence of other risk factors, in order to recommend heterozygous women not to use COC, a more thorough investigation had to be conducted regarding the effects

of abstaining from COC use on unwanted pregnancies, ovarian malignancy, etc. Homozygous carriers, however, were recommended not to use COC because of the very high risk of thrombosis.

There was no difference in unplanned pregnancies needing induced legal abortions between carriers of FV Leiden and noncarriers. Our aim was to not force heterozygous women away from COC without giving them a good alternative. The discussion regarding alternatives was carried out as part of our routine. If acceptable, these women were usually advised to use an intrauterine device, or other gestagen-only methods.

We hope that our investigation will be of use in the ongoing discussion regarding the pros and cons of APC resistance (FV Leiden) testing, and that the information might be of value in a cost-benefit analysis of APC resistance screening.

We concluded that most APC-resistant women want to know their APC resistance status, that there was not an increased incidence of legal abortions, but almost one-third were more worried or afraid of getting pregnant again in consequence of receiving such information.

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