Lifestyle and venous thrombosis

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CHAPTER 5

Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study

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SUMMARY

Background: Venous thrombosis is one of the leading causes of maternal morbidity and mortality.

Objective: In the MEGA study, we evaluated pregnancy and the postpartum period as risk factors for venous thrombosis in 285 patients and 857 control subjects. Patients/Methods: Between March 1999 and September 2004, consecutive patients with a first episode of venous thrombosis were included from six anticoagulation clinics. Partners of patients and a random digit dialing group were included as control subjects. Participants completed a questionnaire and DNA was collected.

Results: The risk of venous thrombosis was five-fold (OR 4.6, 95%CI 2.7-7.8) increased during pregnancy and sixty-fold (OR 60.1, 95%CI 26.5-135.9) increased during the first three months after delivery compared to non-pregnant women. A 14-fold increased risk of deep venous thrombosis of the leg was found compared to a six-fold increased risk of pulmonary embolism. The risk was highest in the third trimester of pregnancy (OR 8.8, 95%CI 4.5-17.3) and during the first six weeks after delivery (OR 84.0, 95%CI 31.7-222.6). The risk of pregnancy-associated venous thrombosis was 52-fold increased in factor V Leiden carriers (OR 52.2, 95%CI 12.4-219.5) and 31-fold increased in carriers of the prothrombin 20210A mutation (OR 30.7, 95%CI 4.6-203.6) compared to non-pregnant women without the mutation.

Conclusion: We found an increased risk of venous thrombosis during pregnancy and the postpartum period, with an especially high risk during the first six weeks postpartum. The risk of pregnancy-associated venous thrombosis was highly increased in carriers of factor V Leiden or the prothrombin 20210A mutation.

INTRODUCTION

Venous thrombosis is one of the leading causes of maternal morbidity and mortality[1, 2]. In developed countries, about 15% of maternal deaths results from pulmonary embolism[3]. In women of reproductive age, over half of all venous thrombotic events are related to pregnancy[4].

A large study of pregnancy associated venous thrombosis is the Glasgow study, a retrospective study of over 72000 deliveries[5]. This study reported an incidence of pregnancy-associated venous thrombosis of 3.24 per 1000 women years, with an incidence of 2.45 per 1000 women years for deep venous thrombosis of the leg and an incidence of 0.79 per 1000 women years for pulmonary embolism. For deep venous thrombosis of the leg the majority of cases (84%) occurred in the left leg, which is in accordance with the findings of other studies[6, 7]. The mechanism behind this propensity for the left leg is still under debate[8]. During pregnancy, the risk was highest during the third trimester[5]. Findings of other studies addressing risk differences in the three trimesters of pregnancy are inconsistent. An equal risk distribution during all three trimesters of pregnancy has been reported but there are also studies showing the highest risk during the first or second trimester of pregnancy[6-10]. The incidence of thrombosis was highest during the first six weeks after delivery both for deep venous thrombosis of the leg and for pulmonary embolism[5]. A higher risk during the postpartum period compared to pregnancy is reported by many other studies[10, 11].

As women with thrombophilia are at increased risk of venous thrombosis, a number of studies have been carried out to study the effect of pregnancy and the postpartum period in these women[12-17]. The most common inherited thrombophilias are the factor V Leiden and the prothrombin 20210A mutation. A meta-analysis of thrombophilias in pregnant women has shown the risk to be over eight-fold higher for heterozygous factor V Leiden carriers and almost seven-fold higher for heterozygous prothrombin 20210A mutation carriers than in pregnant women without thrombophilia[18].

In the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study), a large population-based case-control study, we evaluated pregnancy and the postpartum period as risk factors for venous thrombosis. We were able to identify a sufficient number of patients in their pregnancy or postpartum period to allow for subgroup analyses; we evaluated the pregnancy-associated risk of deep venous thrombosis of the leg and pulmonary embolism separately and also analysed the risk of specific time frames within the pregnant and postpartum period. In addition the joint effect of pregnancy with factor V Leiden and the prothrombin 20210A mutation was addressed.

METHODS

Participants

The MEGA study included consecutive patients with a first diagnosis of venous thrombosis. Between March 1999 and September 2004, patients were recruited from six regional anticoagulation clinics (Amersfoort, Amsterdam, Den Haag, Leiden, Rotterdam and Utrecht) which monitor the anticoagulant therapy of all patients within a well-defined geographical area in the Netherlands. In order to participate, patients were required to be between the age of 18 and 70. Patients with severe psychiatric problems or those unable to speak Dutch were for practical reasons considered ineligible. Within the total patient group the diagnosis of 97% of deep venous thrombosis and 79% of pulmonary embolism was objectively confirmed. Ninety percent of patients used in the final analysis had an objectively confirmed diagnosis. Seven out of 285 patients (2.5%) had no objectively confirmed diagnosis and twenty-one out of 285 patients did not provide permission to obtain their medical records (7.4%). The tests included compression ultrasonography, Doppler ultrasound, impedance plethysmography and contrast venography for diagnosis of deep venous thrombosis and perfusion and ventilation lung scanning, spiral computer tomography and pulmonary angiography for pulmonary embolism.

Partners of patients were asked to participate as control subjects and an additional control group was obtained using the random digit dialing (RDD) method[19]. Only control subjects with no recent history of venous thrombosis were included and the same exclusion criteria as for patients were applied. Details of the MEGA study have been published previously[20].

Of 6055 eligible patients, 5051 participated (83%). Within this group 2737 were women and 2714 provided information on whether they had been pregnant or not before the thrombotic event. Of the 5051 participating patients, 3656 had an eligible partner of whom 2982 participated (82%). An additional 314 partners were included of whom the patient was either excluded for the final analysis, or had deep venous thrombosis of the arm. Thus a total of 3298 partners were willing to participate. Within this group 1665 were women of whom 1645 provided pregnancy related information. Out of 4350 eligible RDD control subjects, 3000 were willing to participate (69%). Information on pregnancy was obtained from 1710 out of 1719 women in this group. Individuals who were over 50 years of age, had no partner, used oral contraceptives or hormone replacement therapy or had malignancy or a partner with malignancy (for patients and partner controls) were excluded from the analyses leading to 285 patients and 857 control subjects.

The study was approved by the Medical Ethics Committee of the Leiden University Medical Center, the Netherlands. Written informed consent was obtained from all participants.

Data collection

Participants completed a detailed questionnaire on risk factors for venous thrombosis. Items covered in the questionnaire included oral contraceptive use, hormone replacement therapy, pregnancies, malignancies and civil status. The questionnaire covered a one year period prior to the index date, i.e. the date of diagnosis of the thrombosis for patients and the date of filling in the questionnaire for partners and the random control subjects. When participants were not willing to or unable to fill in the questionnaire, a standardized mini-questionnaire was taken by telephone, which also included pregnancy related questions. Participants were asked if they had been pregnant in the year before the index date or if they were still pregnant, and what the (expected) date of delivery was. We defined postpartum as the period up to three months after delivery. Information on the location of the affected leg in patients with a deep venous thrombosis of the leg was retrieved from the questionnaire and discharge letters. Out of 285 patients, 176 had a deep venous thrombosis of the leg (with or without pulmonary embolism) of whom 173 had information regarding the affected leg.

DNA collection

Three months after discontinuation of anticoagulant therapy patients and partner controls were invited for an interview and blood draw. In patients who continued anticoagulant therapy for over a year after the event, blood was drawn during anticoagulant therapy. When the participant was unable to come to the clinic a buccal swab was sent. From June 2002 onwards, blood draws were no longer performed in patients and their partners and blood draws were replaced by buccal swabs. Upon completion of the questionnaire, RDD controls were invited for an interview and blood draw. A detailed description of blood collection and DNA analysis for the factor V Leiden (G1691A) and the prothrombin mutation (G20210A) in the MEGA study has been published previously[20].

Within the patient group used for the present analyses 256 provided a blood sample or buccal swab (90%). In the control group 681 blood samples or buccal swabs were obtained (79%). Factor V Leiden and the prothrombin 20210A mutation were successfully determined in all patients and 679 control subjects.

Statistical analysis

As estimates of relative risks odds ratios (ORs) and 95% confidence intervals (95%CI) were calculated according to the method of Woolf. With a multiple logistic regression model we adjusted for age (categorical, seven classes). Because none of the control subjects in the analysis were matched to patients (they were either random population controls or partners of other (male) patients) all analyses were unmatched, with unconditional logistic regression. SPSS for Windows version 12.0.1 (SPSS Inc, Chicago, Ill) was used for all statistical analyses.

RESULTS

A group of 285 women aged 18 to 50 with venous thrombosis and 857 control subjects in the same age group were included in the analysis, with a mean age of respectively 38.3 (5^{th} -95^{th} percentile, 25.7-49.6) and 39.9 years (5^{th} -95^{th} percentile, 27.0-49.8). In the patient group 55% (n=158) was diagnosed with a deep venous thrombosis of the leg, 38% (n=109) with a pulmonary embolism and 6% (n=18) with the combined diagnosis.

Within the patient group, 116 out of 285 women (41%) were pregnant at the time of thrombosis or had been pregnant the three months before the thrombosis, compared to 82 out of 857 (9.6%) control subjects at the index date. The risk of venous thrombosis was five-fold (OR 4.6, 95%CI 2.7-7.8) increased during pregnancy and sixty-fold (OR 60.1, 95%CI 26.5-135.9) increased during the first three months after delivery compared to non-pregnant women (Table 1).

Odds ratios were higher in young women than in older women: in women aged 18 to 29 the risk of venous thrombosis during pregnancy was almost thirteen-fold increased (OR 12.5, 95%CI 4.0-39.5) whereas in women aged 30 to 50 the risk was three-fold increased (OR 3.3, 95%CI 1.8-6.1). Postpartum the risk was also more pronounced in women age 18 to 29 (OR 299.3, 95%CI 49.4-1813.1) than in women aged 30 to 50 (OR 29.4, 95%CI 12.1-71.5) (Table 1).

The risk of venous thrombosis during the first two trimesters of pregnancy appeared to be only slightly increased, with an odds ratio of 1.6. However, the risk was increased nine-fold (OR 8.8, 95%CI 4.5-17.3) during the third trimester compared to non-pregnant women. During the first six weeks after delivery the risk was highest (OR 84.0, 95%CI 31.7 – 222.6). Most cases of venous thrombosis during this period occurred within the first four weeks (95%), with the highest number of cases in the second week (42%) compared to 18%, 20% and 15% in the first, third and fourth week. The risk remained increased up to three months postpartum (Table 2).

Table 1. Relative risk of venous thrombosis during pregnancy and postpartum; overall and by age category

Age group (yrs)	Status	Patients (n)	Control subjects (n)	OR*	95%CI
18 to 50	Neither	169	775	1	Ref.
	Pregnant[†]	36	58	4.6	2.7-7.8
	Postpartum[‡]	69	10	60.1	26.5-135.9
	Overall[§]	116	82	9.7	6.4-14.9
18 to 29	Neither	7	86	1	Ref.
	Pregnant	14	18	12.5	4.0-39.5
	Postpartum	34	3	299.3	49.4-1813.1
30 to 50	Neither	162	689	1	Ref.
	Pregnant	22	40	3.3	1.8-6.1
	Postpartum	35	7	29.4	12.1-71.5

Ref., Reference category; OR, odds ratio; 95%CI, 95% confidence interval
*adjusted for age
[†]four women who currently were and had previously been pregnant are included in the pregnant group
[‡]period up to 3 months after delivery [§]included the pregnant and postpartum category and an additional 11 cases and 14 control subjects of whom delivery dates were unavailable

Table 2. Relative risk of venous thrombosis by different stages of pregnancy and postpartum

Status	Patients		Control subjects		OR*	95%CI
	n	(%)	n	(%)		
Neither	167	60.9	735	87.2	1	Ref.
1st and 2nd trimester	8	2.9	36	4.3	1.6	0.7-3.7
3rd trimester	28	10.2	22	2.6	8.8	4.5-17.3
1 to 6 weeks postpartum	66	24.1	6	0.7	84.0	31.7-222.6
7 weeks to 3rd month postpartum	3	1.1	4	0.5	8.9	1.7-48.1
4th month to 1 year postpartum	2	0.8	40	4.7	0.3	0.1-1.4

Ref., Reference category; OR, odds ratio; 95%CI, 95% confidence interval
*adjusted for age
Note: Information on delivery dates was unavailable for 11 cases and 14 controls

Overall pregnancy associated risk was most pronounced for deep vein thrombosis of the leg (OR 14.3; 95%CI 8.3-24.5) and six-fold increased for pulmonary embolism (OR 5.8; 95%CI 3.3-10.3. During pregnancy, the risk of deep venous thrombosis of the leg was clearly increased (OR 7.8; 95%CI 4.1-15.0), whereas that of pulmonary embolism was at most weakly increased (OR 2.3; 95%CI 1.0-5.2). In the postpartum period the risk for both was increased, with a relative risk of 72.6 for deep venous thrombosis of the leg and a relative risk of 34.4 for pulmonary embolism (Table 3).

The majority of pregnancy-associated deep venous thrombosis cases occurred in the left leg. During pregnancy 85% of women (23 out of 27) had a left-sided deep venous thrombosis, compared to 68% (32 out of 47) of women in the postpartum

Table 3. Risk of deep venous thrombosis, pulmonary embolism and the combined diagnosis by pregnancy status

	Patients (n)	Control subjects (n)	OR*	95%CI
DVT				
Neither	83	775	1	Ref.
Pregnant	27	58	7.8	4.1-15.0
Postpartum	42	10	72.6	30.1-175.4
Overall[†]	75	82	14.3	8.3-24.5
PE				
Neither	73	775	1	Ref.
Pregnant	9	58	2.3	1.0-5.2
Postpartum	22	10	34.4	13.3-88.5
Overall[‡]	36	82	5.8	3.3-10.3
DVT+PE				
Neither	13	775	1	Ref.
Pregnant	0	58	--	--
Postpartum	5	10	46.4	10.0-214.7
Overall[§]	5	82	5.5	1.4-21.1

DVT, deep venous thrombosis of the leg; PE, pulmonary embolism; Ref., Reference category; OR, odds ratio ; 95%CI, 95% confidence interval; *adjusted for age

[†]included the pregnant and postpartum category and an additional 6 cases and 14 control subjects of whom delivery dates were unavailable

[‡]included the pregnant and postpartum category and an additional 5 cases and 14 control subjects of whom delivery dates were unavailable

[§]included the pregnant and postpartum category and an additional 14 control subjects of whom delivery dates were unavailable

Table 4. The joint effect of pregnancy status and the factor V Leiden mutation (FVL) or the prothrombin 20210A (FII) mutation

Pregnant or postpartum	FVL	Patients (n)	Control subjects (n)	OR*	95%CI
-	-	144	580	1	Ref.
+	-	81	56	8.6	5.2-14.3
-	+	12	40	1.3	0.6-2.5
+	+	19	3	52.2	12.4-219.5
	FII				
-	-	141	605	1	Ref.
+	-	94	57	10.1	6.2-16.4
-	+	15	15	4.4	2.1-9.4
+	+	6	2	30.7	4.6-203.6

Ref., Reference category; OR, odds ratio; 95%CI, 95% confidence interval
*adjusted for age

period. In women who were not pregnant the right-left distribution was almost even, with 53% (52 out of 99) diagnosed with a left-sided deep venous thrombosis.

Among non-carriers of factor V Leiden, pregnancy and the postpartum period resulted in a nine-fold increased risk of venous thrombosis (OR 8.6, 95%CI 5.2-14.3). The joint effect of factor V Leiden and pregnancy resulted in a 52-fold

increased risk (OR 52.2, 95%CI 12.4-219.5), compared to non-carriers who had not been pregnant (Table 4). The risk of pregnancy-associated venous thrombosis was 31-fold increased (OR 30.7, 95%CI 4.6-203.6) in carriers of the prothrombin 20210A mutation, compared to non-pregnant, non-carriers (Table 4).

DISCUSSION

In this population-based case-control study we found a five-fold increased risk of venous thrombosis during pregnancy and a sixty-fold increased risk of venous thrombosis in the postpartum period. The risk was especially high during the first six weeks after delivery. The risk of both deep venous thrombosis of the leg and pulmonary embolism was increased during pregnancy and the postpartum period. During pregnancy venous thrombosis occurred far more often in the left than in the right leg. In carriers of the factor V Leiden mutation the risk of pregnancy-associated venous thrombosis increased markedly to about 52-fold compared to non-carriers who had not been pregnant. A somewhat lower increase in risk was found in prothrombin 20210A carriers, in whom the risk was 31-fold increased, compared to non-carrying, non-pregnant women.

Our finding of a five-fold increased risk in women who were pregnant is in accordance with the results of other studies[10, 11]. The higher relative risks of pregnancy in younger women compared to older women were in contrast with previous follow-up studies. However, one should bear in mind the difference between relative and absolute risks. Since thrombosis is age-dependent, these two will never both be constant over age, and a similar absolute increase will lead to much higher relative risks in young than in older women. Hence, one cannot conclude from our data that the influence is lower in older than in younger women and the reverse is probably true, also based on these data.

While previous reports were conflicting about the risk per trimester of pregnancy[6-10], we found the highest risk during the third trimester. These findings should be interpreted with some caution, because the higher risk during the third trimester might reflect a relatively high number of misdiagnoses in this trimester due to compression issues by the gravid uterus that leads to symptoms similar to venous thrombosis[8]. However, this is not very likely in our study, since 97% of patients with deep venous thrombosis were objectively diagnosed. A more important consideration is the inclusion of patients through anticoagulation clinics. Some women with venous thrombosis during pregnancy are initially treated without involvement of the anticoagulation clinic and receive low molecular weight heparin (LMWH). Women who had their venous thrombosis during the first or second trimester are

more likely to be treated with LMWH only than women with a venous thrombosis during the third trimester, who are referred to the anticoagulation clinic for additional treatment after child delivery. This might have led to an underestimate of the risk of thrombosis during early stages of pregnancy, thus no firm conclusion can be drawn about lower risks in the first two trimesters compared with the third trimester.

The risk of venous thrombosis during the first six weeks after delivery was very high compared to the overall pregnancy-associated risk. Our finding of a 84-fold higher risk during this period is within the range of findings from the majority of other studies, that reported a two- to fifteen-fold increased risk during the first six weeks after delivery compared to pregnancy[7, 14, 21]. The Glasgow study found 2.51 cases of venous thrombosis per 1000 person years in the first six weeks after delivery[5]. When we contrast this figure to the baseline risk of venous thrombosis of 0.08 per 1000 in these young women[22], these data point to a relative risk of 31 during this period. A case-control study in which control subjects were subject to the same referral and diagnostic procedures as patients found, however, less difference in the thrombotic risks during the first month after delivery and pregnancy[23]. A high risk of venous thrombosis during the first weeks after delivery may be explained by coagulation changes due to operative delivery, postnatal infections or immobility[24].

For a correct calculation of relative risks during different stages of pregnancy and the postpartum period it is important that the proportion of control subjects in each time frame is a good reflection of the source population. To verify this, we calculated the expected number of controls in each period, using data from the general population[25]. The percentage of pregnant or postpartum women was higher in the random digit dialing control group (12.3%) than in the partner control group (3.8%). In the overall control group the prevalence of pregnant or postpartum women (8.1%) was similar to the general population (8.8%). During pregnancy the proportion of controls was similar to what we would expect to find (6.9% compared to an expected 6.6%). In the first three months postpartum we observed a lower proportion of controls (1.2% compared to an expected 2.2%), possibly due to a reduced motivation to participate in our study after child delivery. In the period from four months up to one year postpartum the proportion of controls was still somewhat reduced (4.7% compared to an expected 6.6%). These lower proportions have probably resulted in a slight overestimation of relative risks in the postpartum period.

Furthermore, the time needed for control subjects to return the questionnaire could have influenced the percentage of pregnant controls assigned to each period. As controls returned the questionnaire more quickly than patients and 61% of the

controls had replied within a week (86% within a month) this is unlikely to have affected results.

Not much is known about the relative risks of the separate diagnoses of deep venous thrombosis of the leg and pulmonary embolism, during and after pregnancy. An American cohort study reported an increased risk of deep venous thrombosis and pulmonary embolism during pregnancy. Postpartum the risks were further increased with a four-fold higher risk of deep venous thrombosis and a 15-fold increased risk of pulmonary embolism compared to the pregnant period[10]. Also a Danish cohort study reported an increased risk of both deep venous thrombosis and pulmonary embolism during pregnancy and the first six weeks after delivery, with again a higher risk of pulmonary embolism during the postpartum period compared to the pregnant period[26]. We found increased risks of deep venous thrombosis of the leg and pulmonary embolism postpartum, while during pregnancy the risk of pulmonary embolism was only slightly increased.

When analysing the combined effect of pregnancy and the postpartum period with the factor V Leiden mutation or the prothrombin 20210A mutation, we found substantial increased risks for the combination of these risk factors. A meta-analysis of thrombophilias in pregnancy has found an eight-fold higher risk for heterozygous factor V Leiden carriers and an almost seven-fold higher risk for heterozygous prothrombin 20210A mutation carriers than pregnant women without thrombophilia[18]. Performing our analysis within pregnant women only, we found a five-fold increased risk for factor V Leiden carriers and a two-fold increased risk for prothrombin 20210A carriers.

In these young women, we found a low relative risk of 1.3 in carriers of factor V Leiden who had not been pregnant, which is lower than the overall risk of venous thrombosis due to factor V Leiden (three- or more fold increased)[27]. To investigate if the low risk was due to a too large proportion of non-pregnant factor V Leiden carriers among control subjects, we calculated the relative risk of venous thrombosis that one would expect in these control subjects using data from the general Dutch population as control situation. Using general data on live birth, stillbirth and use of oral contraceptives we calculated that 8.8% of these young women were expected to be pregnant or in the postpartum period[25]. Together with a prevalence of 5% for factor V Leiden[28], the calculated relative risk would be 1.5 in carriers of factor V Leiden compared to non-carriers who had not been pregnant; a similar relative risk as our finding (with 144 patients of the reference category and the 12 non-pregnant patients with factor V Leiden the following calculation was performed: 144*(5*(1-0.088)/95*(1-0.088))=7.76, 12/7.76=1.5).

We performed several subgroup analyses with relatively small numbers of patients and control subjects. Several confidence intervals were wide, but results were

in accordance with previous studies and the lower boundaries of many confidence intervals were above 2.1, with odds ratios of 4.4 or higher, indicating that the true effects were likely to be substantial.

A limitation of our study was the absence of data on the mode of delivery. It would have been interesting to investigate if we could replicate or refute previous findings that reported an increased risk of venous thrombosis from vaginal delivery to elective caesarean section to emergency caesarean section[2].

In conclusion, we found an increased risk of venous thrombosis during both pregnancy and the postpartum period, with an especially high risk during the first six weeks after delivery. Women with either factor V Leiden or prothrombin 20210A thrombophilia had a substantially increased risk of pregnancy-associated venous thrombosis compared to women without these mutations.

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