D-Dimer Testing in Pregnancy

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Key Words

D-Dimer · Pregnancy

Abstract

During pregnancy, elevated markers of coagulation and fibrinolytic system activation, such as D-Dimer, indicate increased thrombin activity and increased fibrinolysis following fibrin formation. Testing for D-Dimer during pregnancy could therefore be useful for the diagnosis and prediction of a venous thromboembolic event (VTE) or pregnancy-related complications, and for monitoring antithrombotic treatment. This approach, however, is hampered by the fact that even an uncomplicated pregnancy in healthy women is accompanied by a substantial increase of D-Dimer. Thus, prior to clinical application reference values of D-Dimer according to gestational age need to be established. A substantial increase of D-Dimer during pregnancy is seen despite thromboprophylaxis with low molecular weight heparin (LMWH) indicating that further studies are needed to evaluate monitoring of LMWH during pregnancy and to investigate the optimal beginning and dose of LMWH thromboprophylaxis in pregnant women.

During normal pregnancy both the risk of bleeding and of thrombosis are increased. While bleeding complications mainly occur during or after delivery, the risk of thrombosis is increased throughout pregnancy and is particularly high after delivery. Altered rheology, vascular injury, impaired fibrinolysis and a hypercoagulable state contribute to the increased risk of venous thrombosis. This is also reflected by various alterations of the hemostatic system which occur during normal pregnancy, such as elevated levels of factors VII, VIII, X and von Willebrand antigen [1]. In addition, we have demonstrated that even uncomplicated pregnancy is accompanied by a substantial hemostatic system activation as indicated by an increase in the plasma concentration of coagulation activation markers, such as prothrombin fragment F1+2 and D-Dimer [2].

The elevated levels of D-Dimer during pregnancy may reflect (1) increased coagulation activation and thrombin generation, (2) increased fibrinolysis, or (3) a combination of both. Consequently, testing for D-Dimer during pregnancy could be useful for the diagnosis and prediction of a venous thromboembolic event (VTE) or pregnancy-related complications, and for monitoring antithrombotic treatment.

Diagnosis of Venous Thromboembolism

Although D-Dimer testing has a prominent role in the exclusion of acute venous thrombosis in the non-pregnant

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population [3, 4], incorporating D-Dimer in algorithms for diagnosing VTE in pregnant women has not been adequately studied. This approach is mainly hampered by the fact that even during an uncomplicated pregnancy in healthy women D-Dimer levels increase with gestational age [2, 5-7]. Therefore, prior to clinical application, reference values for D-Dimer according to gestational age need to be established. These reference values need to be calculated in an adequate number of healthy pregnant women of different gestational weeks [8]. Subsequently, the specificity and sensitivity of various cut-off levels of D-Dimer for the diagnosis of VTE during pregnancy need to be tested. As long as these data are not available, D-Dimer has very limited value in the diagnosis of venous thrombosis during pregnancy.

Prediction of Venous Thromboembolism

Although infrequent, VTE during pregnancy is an important cause of maternal death in the industrialized world. Women with prior VTE are believed to have a higher risk of VTE in a subsequent pregnancy. Currently, there are only two studies, in which the risk of recurrence and the association with potential risk factors have been evaluated [9,10]. In the prospective study, the frequency of antepartum recurrences was 2.4% [9]. In neither of the two studies, a clear prediction of women at risk by testing for traditional thrombophilic risk factors was possible. D-Dimer is a good predictor of recurrent venous thromboembolism in non-pregnant patient cohorts [11, 12]. Low levels of D-Dimer were associated with a 60% reduction of the relative risk of recurrence compared to patients with higher levels which was independent of other thrombotic risk factors [12]. Importantly, the prevalence of markers of thrombophilia, such as factor V Leiden, prothrombin G20210A, or high factor VIII, was significantly higher among patients with high D-Dimer as compared with those with low levels. Thus, D-Dimer testing during pregnancy could be useful to identify women at high risk of (recurrent) venous thrombosis. Adequately designed studies are warranted to investigate this issue and the timing of D-Dimer testing as well as the appropriate cut-off levels in pregnant women.

Diagnosis and Prediction of Pregnancy Related Complications

Several studies have investigated whether pregnancy related complications, such as gestational hypertension [13] and diabetes [14], preeclampsia [15, 16], or abruptio placentae [17], are associated with changes in hemostatic parameters. Interpretation of the studies, however, is limited

by several facts: (1) pregnancy related complications comprise a variety of clinical entities, which often leads to the inclusion of inhomogeneous patient cohorts, (2) the number of patients in these studies was small as was the number of controls, (3) since reference values of D-Dimer during normal pregnancy are not available, the specificity of D-Dimer for diagnosing and predicting pregnancy related complications is reduced.

Monitoring of Antithrombotic Treatment

Several studies indicate that low-molecular weight heparin (LMWH) is safe and effective during pregnancy [18-20]. Clinical thromboprophylactic as well as therapeutic trials comparing LMWH and unfractionated heparin included many thousands of patients and were safely conducted without monitoring LMWH. Summarizing the results of these studies, monitoring of LMWH by measuring anti-Xa levels did not improve the safety and efficacy of LMWH. In addition, anti-Xa measurement in plasma has potential pitfalls, such as the different anti-Xa/anti-IIa ratios of the LMWH preparations, or the timing of blood sampling. There are, however, some situations including over- or underweight patients or renal insufficiency, in which monitoring of LMWH is recommended. During pregnancy, the need to adapt LMWH to the weight of the pregnant woman has never been studied in appropriate trials and remains controversial. In addition, firm recommendations with regard to either the timing of the monitoring or adapting the dosage of LMWH are not available.

In a prospective study, we measured D-Dimer throughout pregnancy in women who received LMWH thromboprophylaxis and in healthy pregnant controls [21]. Despite LMWH, activation of the coagulation system was already seen during the early course of pregnancy, and further substantial coagulation activation occurred with advancing pregnancy. One of 61 women who received LMWH after previous VTE had recurrence. Further studies are needed to evaluate monitoring of LMWH during pregnancy and to investigate the optimal beginning and dose of LMWH thromboprophylaxis in pregnant women.

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