Protein Z Deficiency and Pregnancy Outcomes

1. Protein Z, an anticoagulant protein with expanding role in reproductive biology.

**Author(s):** Almawi, Wassim Y; Al-Shaikh, Fatima S; Melemedjian, Ohannes K; Almawi, Ahmad W

**Source:** Reproduction (Cambridge, England); Aug 2013; vol. 146 (no. 2); p. R73

**Publication Date:** Aug 2013

**Publication Type(s):** Journal Article Review

**PubMedID:** 23690629

Available at Reproduction - from HighWire - Free Full Text

**Abstract:** Protein Z (PZ) is a vitamin K-dependent factor characterized by its homology to other vitamin K-dependent factors (factors VII, IX, and X, protein C and protein S), but lacks any enzymatic activity. Instead, PZ acts as a cofactor for the inhibition of factor Xa through the serpin PZ-dependent protease inhibitor (ZPI). PZ deficiency is associated with a procoagulant state, highlighted by excessive FXa secretion and thrombin production, and is linked with several thrombotic disorders, including arterial vascular and venous thromboembolic diseases. A role for the PZ-ZPI complex in the regulation of physiological pregnancy has been demonstrated, highlighted by the progressive elevation in PZ levels in the first trimester of gestation, which then steadily decline toward delivery. An association between altered plasma PZ concentrations and adverse pregnancy outcomes (recurrent miscarriage, stillbirth, preeclampsia, intrauterine growth restriction, and placental abruption) has been reported. The mechanism by which PZ deficiency leads to adverse pregnancy outcomes is not clear, but it is multifactorial. It may be attributed to the anti-PZ IgG and IgM autoantibodies, which apparently act independently of classical antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein I antibodies). PZ deficiency has also been reported to be constitutional, and a number of variants in the PROZ (PZ) gene and SERPINA10 (ZPI) gene are linked with specific adverse pregnancy complications. This review summarizes the relationship between adverse pregnancy outcomes and acquired and constitutional PZ-ZPI deficiency, in order to understand whether or not PZ deficiency could be considered as a risk factor for poor pregnancy outcomes.

**Database:** Medline
2. A meta-analysis of potential risks of low levels of protein Z for diseases related to vascular thrombosis.

Author(s): Sofi, Francesco; Cesari, Francesca; Abbate, Rosanna; Gensini, Gian Franco; Broze, George; Fedi, Sandra

Source: Thrombosis and haemostasis; Apr 2010; vol. 103 (no. 4); p. 749-756

Publication Date: Apr 2010

Publication Type(s): Meta-analysis Journal Article Review

PubMedID: 20076855

Available at Thrombosis and Haemostasis - from PubMed Central

Abstract: The relationship between protein Z levels and thrombosis is controversial. We performed a systematic review and meta-analysis of the available studies to assess the association between protein Z and vascular thrombotic diseases. We conducted an electronic literature search through MedLine, Embase, Google Scholar, Web of Science, The Cochrane Library, bibliographies of retrieved articles and abstracts of congresses up to October, 2009. Studies were included if they analysed protein Z levels in patients with vascular thrombotic diseases. After the review process, 28 case-control studies (33 patient cohorts), including 4,218 patients with thrombotic diseases and 4,778 controls, were selected for analysis. The overall analysis using a random-effects model showed that low protein Z levels were associated with an increased risk of thrombosis (odds ratio [OR] 2.90, 95% confidence interval [CI] 2.05-4.12; p<0.00001). On subgroup analysis, a significant association was found between low protein Z levels and arterial vascular diseases (OR 2.67, 95%CI 1.60-4.48; p=0.0002), pregnancy complications (OR 4.17, 95%CI 2.31-7.52; p<0.00001), and venous thromboembolic diseases (OR 2.18, 95%CI 1.19-4.00; p=0.01). The results of this meta-analysis are consistent with a role for protein Z deficiency in thrombotic diseases, including arterial thrombosis, pregnancy complications and venous thromboembolism.

Database: Medline
3. Protein Z variants associated with protein Z plasma levels and with risk of idiopathic recurrent miscarriage.

**Author(s):** Al-Shaikh, Fatima S; Sater, Mai S; Finan, Ramzi R; Racoubian, Eddie; Abu-Hijleh, Tala M; Mustafa, Fekria E; Almawi, Wassim Y

**Source:** Reproductive sciences (Thousand Oaks, Calif.); Sep 2013; vol. 20 (no. 9); p. 1062-1068

**Publication Date:** Sep 2013

**Publication Type(s):** Journal Article

**PubMedID:** 23420821

**Abstract:** Protein Z (PZ) deficiency due to anti-PZ autoantibodies and/or mutations in PZ gene was linked with adverse pregnancy outcomes, including idiopathic recurrent miscarriage (IRM). We investigated the association of rs3024718, rs3024719, rs3024731, rs3024778, rs3024772, and rs3024735 (G79A) PZ variants and changes in PZ levels in 287 women with IRM, and 308 control women. Of the 6 single nucleotide polymorphisms (SNPs) analyzed, higher minor allele frequency of rs3024735 (G79A) and rs3024731 were seen in IRM cases than in control women. Significantly higher frequencies of rs3024735/G79A G/A and A/A (P< .001), rs3024719 G/A (P= .009), and rs3024731 A/A (P = .012), but not rs3024718 (P= .12), rs3024778 (P = .76), or rs3024772 (P= .27) genotype carriers were seen between IRM cases versus control women, respectively, and was linked with reduced PZ levels. Six-locus (rs3024718/rs3024719/rs3024778/rs3024731/rs3024735/rs3024772) PZ haplotypes analysis demonstrated increased frequency of GAGAAG and AGGTAG and reduced frequency of AGGTGC haplotypes in IRM cases, thereby conferring disease susceptibility and protective nature to these haplotypes, respectively. These results demonstrate that specific PZ SNPs and haplotypes are significantly associated with IRM.

**Database:** Medline


**Author(s):** Caliandro, R; Nico, G; Tiscia, G; Favuzzi, G; De Stefano, V; Rossi, E; Margaglione, M; Grandone, E

**Source:** Thrombosis and haemostasis; Sep 2013; vol. 110 (no. 3); p. 534-542

**Publication Date:** Sep 2013

**Publication Type(s):** Multicenter Study Journal Article

**PubMedID:** 23846529

**Abstract:** The role of protein Z (PZ) in the etiology of human disorders is unclear. A number of PZ gene variants, sporadic or polymorphic and found exclusively in the serine protease domain, have been observed. Crystal structures of PZ in complex with the PZ-dependent inhibitor (PZI) have been recently obtained. The aim of this study was a structural investigation of the serine protease PZ domain, aiming at finding common traits across disease-linked mutations. We performed 10-20 ns molecular dynamics for each of the observed PZ mutants to investigate their structure in aqueous solution. Simulation data were processed by novel tools to analyse the residue-by-residue backbone flexibility. Results showed that sporadic mutations are associated with anomalous flexibility of residues belonging to specific regions. Among them, the most important is a loop region which is in contact with the longest helix of PZI. Other regions have been identified, which hold anomalous flexibility associated with potentially protective gene variants. In conclusion, a possible interpretation of effects associated with observed gene variants is provided. The exploration of PZ/PZI interactions seems essential in explaining these effects.

**Database:** Medline
5. Protein Z deficiency and Lipoprotein (a) increase are the most frequent abnormalities in women with recurrent miscarriage

Author(s): Bergmann F.; Groening H.; Frohne S.; Guenther F.; Luttkus K.; Czwalinna A.

Source: Journal of Thrombosis and Haemostasis; Jul 2013; vol. 11; p. 868

Publication Date: Jul 2013

Publication Type(s): Conference Abstract

Abstract: Introduction: More than 1-2% of women suffer from recurrent miscarriage (RM), vascular complications of pregnancy or implantation failure after assisted reproduction. Guidelines recommend ruling out chromosomal or anatomical abnormalities as well as antiphospholipid syndrome or thyroid dysfunction. In Europe, complete thrombophilia work up is commonly requested. By metaanalysis hereditary thrombophilia (e.g. FV-Leiden/-prothrombinmutation) is questionable in RM. However, low Protein Z (PZ)-levels (<1000 mug/L) (inherited or acquired due to antibodies) are associated with vascular complications in pregnancy (OR 4.17) (Sofi 2010). Lp(a) influences the fibrinolytic system which is important in implantation and placental development and elevated Lp(a) (>30 mg/dL) has been reported in women with vascular complications in pregnancy (e.g. preeclampsia). Elevated FVIII is not associated with poor pregnancy outcome (Middledorp 2004).

Material and Methods: Over 1 year 107 women, median age 32 years, were transferred to our coagulation outpatient clinic to rule out hypercoagulability in women with RM. In all women laboratory work up consists of: TSH, Lp(a), Homocysteine (fasting level), FV-Leiden and Prothrombinmutation, Antithrombin, Protein C, free Protein S, Protein Z, FXII, Lupusanticoagulant (dRVVT, PTT-LA), Anti-Cardiolipin IgG and IgM, Anti-beta2-GPI IgG, Anti-Prothrombin IgG and Anti-Phosphatidylserine IgG; BMI calculation and medical history, also in complete pregnancy, were documented. Results: In 32% of our cohort no laboratory abnormality could be detected. 13% had at least two abnormalities. FV-Leiden/-prothrombinmutation were present in 7%, no Antithrombin deficiency; Protein C and S deficiency in 3% and low FXII-levels in 2% and antiphospholipid syndrome in 6%. Hyperhomocysteinemia was detected in 2%. Decreased Protein Z was detected in 20% and Lp(a) >30 mg/dL in 16%. Mean BMI 24.8 (range 17.6-39.1). Abnormal thyroid function was present only in 3%, while some women were already on thyroid medication when investigated. Discussion: RM is a multifactorial disorder; increased maternal age, BMI, thyroid function as well certain coagulation abnormalities influence pregnancy outcome. The frequency of FV-Leiden/-prothrombinmutation as well as hereditary deficiency of Protein C and S and FXII deficiency reflects the prevalence found in normal population and therefore cannot be causal in RM, solely. In our cohort low PZ-levels and elevated Lp(a) were the most frequent abnormalities. Such risk factors may have a potent influence on early implantation and placental development. The question remains, which treatment options are feasible: preconceptional ASA and/or LMW Heparin as in women with APS?

Database: EMBASE
6. Protein Z-deficiency in unexplained affinity to thromboses, bleedings or abortions

Author(s): Radtke H.; Kiesewetter H.; Jainz A.; Schmidt F.-P.

Source: Hamostaseologie; 2012; vol. 32 (no. 1)

Publication Date: 2012

Publication Type(s): Conference Abstract

Abstract: A protein Z-deficiency is presumably related with a 3-fold risk of venous and arterial thrombosis. Mucosal bleedings and post-operative haematomas can occur more frequently. This is seen in an increased in vivo bleeding time without other plasmatic coagulation disorders or thrombopathies. Pregnancy complications, especially abortions before the 15th week of gestation, are described as well. Since May 2011 the plasmatic concentration of protein Z has been tested in 680 patients of the Hamostaseologicum. In 74 patients a protein Z-deficiency has been found. In other 45 patients protein Z was reduced because of the use of Phenprocoumon or Coumadin. Of the 74 patients with diminished protein Z concentration 39 were marginally decreased (protein Z 1000-1500 mug/l). Of the 35 patients with a protein Z concentration below 1000 mug/l 12 had had a thrombosis before (6 strokes, 3 DVT or PE, 1 arterial thrombosis, 1 retinal branch vein occlusion, 1 acute hearing loss). 7 had arterial hypertension, 2 suffered from diabetes mellitus. Of the patients who had a thrombosis 6 had a heterozygous factor V Leiden mutation. 10 had a microcirculation disorder (Raynaud’s phenomenon). 4 had had bleeding complications before, 3 had a von Willebrand disease Type I, 6 patients had had abortions and 4 were healthy. Of the 39 patients with protein Z concentrations between 1000 and 1500 mug/l 18 had experienced a thrombosis before (9 DVT or PE, 3 myocardial infarctions, 1 CHD, 3 strokes, 1 retinal branch vein occlusion, 1 PAD I, 1 tinnitus). 5 additionally had arterial hypertension. 13 suffered from Raynaud’s phenomenon, of which 7 had a hypotension. Of the patients with thromboses 3 had a heterozygous factor V Leiden mutation and one a protein C-deficiency. 7 patients had had an abortion before. Bleeding complications were seen in 4 patients, of which 3 suffered from von Willebrand disease Type I. It is possible to optimize the haemostaseologic therapy by knowing the protein Z concentration.

Database: EMBASE
7. Increase in the plasma levels of protein Z-dependent protease inhibitor in normal pregnancies but not in non-pregnant patients with unexplained recurrent miscarriage.

Author(s): Souri, Masayoshi; Sugiura-Ogasawara, Mayumi; Saito, Shigeru; Kemkes-Matthes, Bettina; Meijers, Joost C M; Ichinose, Akitada

Source: Thrombosis and haemostasis; Mar 2012; vol. 107 (no. 3); p. 507-512

Publication Date: Mar 2012

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

PubMedID: 22274138

Abstract: Protein Z (PZ)-dependent protease inhibitor (ZPI) is a serine protease inhibitor which efficiently inactivates activated factor X, when ZPI is complexed with PZ in plasma. Reduced plasma levels of ZPI and PZ have been reported in association with thrombosis. It has also been reported that PZ increases during pregnancy and that its partial deficiency is related to early pregnancy loss or recurrent miscarriage (RM). However, until now there has been no report on ZPI in pregnancy. To explore the possible role(s) of ZPI in the maintenance of pregnancy, we studied 42 non-pregnant normal women, 32 women with normal pregnancies, and 134 cases of unexplained RM in Japan, as well as 64 non-pregnant normal German females. Plasma ZPI was measured by in-house ELISA. There were significantly higher concentrations of plasma ZPI in normal pregnancies compared to non-pregnant women. The present study also confirmed that both factor X, the major target of ZPI, and protein Z increased during normal pregnancies. This increased ZPI and PZ may counteract the increased activated factor X, which may in turn contribute to the maintenance of normal placental circulation. Plasma ZPI levels were unchanged in non-pregnant RM women, while the plasma PZ level was slightly reduced, a finding consistent with existing reports. The exact relationship between RM and this unaltered ZPI with mild PZ reduction relative to normal pregnancies warrants further investigation.

Database: Medline

Author(s): AlShaikh, F S; Finan, R R; Almawi, A W; Mustafa, F E; Almawi, W Y

Source: Molecular human reproduction; Mar 2012; vol. 18 (no. 3); p. 156-160

Publication Date: Mar 2012

Publication Type(s): Journal Article

PubMedID: 22039093

Available at Molecular Human Reproduction - from HighWire - Free Full Text
Available at Molecular Human Reproduction - from PubMed Central

Abstract: Protein Z-dependent protease inhibitor (ZPI) is a 72 kDa single-chain serpin which inhibits the activated coagulation factors X and XI. Two non-sense polymorphisms of ZPI, R67X and W303X, were recently identified, and were linked with a prothrombotic state. Here, we investigated the association of the R67X (728C>T) and W303X (1438G>A) variants in the ZPI gene with recurrent spontaneous miscarriage (RSM). This was a case-control study involving a total of 288 women with a history of two consecutive or ≥3 non-consecutive pregnancy losses between 8 and 12th week of gestation, along with 304 age-matched and ethnically matched multiparous control women, with no personal or family history of pregnancy complications. The minor allele frequency of R67X (P = 0.003) and W303X (P = 0.014) were higher in RSM cases than in control women. Both single-nucleotide polymorphisms were significantly associated with RSM under the dominant genetic association model, and were in moderate linkage disequilibrium (D’ = 0.412; P < 0.001). Taking the common (728)C/(1438)G haplotype as reference, multivariate analysis confirmed the positive association of (728)T/(1438)G [P = 0.043; odds ratio (OR) = 2.25; 95% confidence interval (CI) = 1.03-4.90], and (728)T/(1438)A (P = 0.022; OR = 3.93; 95% CI = 1.23-12.59) haplotypes with increased RSM risk. These differences remained significant after controlling for some covariates. These results demonstrate that both ZPI R67X and W303X non-sense variants and specific ZPI haplotypes are significantly associated with RSM.

Database: Medline
9. Protein Z deficiency in patients with pregnancy complications

**Author(s):** Platzer C.; Czwalinna A.; Bergmann F.

**Source:** Hamostaseologie; 2011; vol. 31 (no. 1)

**Publication Date:** 2011

**Publication Type(s):** Conference Abstract

**Abstract:**
Introduction: Protein Z (PZ) has two functions in hemostasis: together with factor Xa it forms an inhibiting complex with the PZ dependent protease inhibitor and it enhances binding of thrombin to phospholipid surfaces. Therefore, low PZ levels may facilitate thrombosis or bleeding.

Aim of the study: To evaluate if low PZ levels are associated with pregnancy complications (early or late fetal loss, IUGR, fetal death), we reviewed data of pts referred to our laboratory. PZ determination is part of our diagnostic work up (whole blood count, PT, PTT, exclusion of antiphospholipid syndrome, Lp(a), ATIII, Protein C and S, homocysteine, FV Leiden, prothrombin mutation). Material and Methods: Over a 1 year period we investigated PZ level in 125 pts. PZ concentration was determined by ELISA (Asserachrom, Diagnostica Stago). Our normal range (881-2724, mean 1744 mug/l) is based on 68 healthy donors; PZ < 1000 mug/l is considered to be abnormal. Results: In 45/111 (40.5 %) pts with pregnancy complications, no coagulation abnormality was detected. In 22/111 (19.8 %) low PZ level was the only abnormality (mean=673, range 283-956 mug/l). 44/111 (39.7 %) were diagnosed with different abnormalities: cardiolipin antibodies (n=3), borderline results for lupus anticoagulant (n=2), high Lp(a) (n=19), factor V Leiden (n=6), prothrombin mutation (n=2), elevated fasting homocysteine (n=4) and thrombocytosis (n=1). 19 pts showed a combination of such above mentioned risk factors, low PZ levels included (n=12).

Conclusion: In 19.8 % of pts with pregnancy complications no other abnormality besides PZ deficiency was detected. Therefore, we consider PZ determination a useful parameter in patients with pregnancy complication after ruling out more common disorders. A recent meta-analysis by Sofi et al (Thromb Haemostas 2010) supports this association. Low PZ levels should be considered to be a cofactor for or a consequence of pregnancy loss and might be a coagulopathy in some pts.

**Database:** EMBASE
Protein Z (PZ) is a vitamin K-dependent factor identified in human plasma in 1984 characterized by an homology with other vitamin K-dependent factors. PZ acts as the cofactor of the PZ dependent inhibitor (ZPI), in the inhibition of activated factor X bound on phospholipid surface. In humans, PZ is characterized by an unusual wide distribution in plasma partly explained by a genetic control. Several PZ gene polymorphisms influencing plasma concentration have been described. In mice, the disruption of PZ gene is asymptomatic, but in association with homozygous FV Leiden produced a severe prothrombotic phenotype. This review analyzes the results obtained from different studies so far published in order to understand whether PZ deficiency could be considered as a risk factor for venous thrombosis. The roles of PZ plasma level and PZ gene polymorphisms remain debated with conflicting results. Many of these studies reported low PZ levels in association with an increased risk of venous thrombosis. On the other side, some studies did not observe an association between low levels of PZ and thrombotic events. A relationship between PZ deficiency and pregnancy complications was also described but not confirmed by all studies. These discrepancies can be explained by the heterogeneity of populations chosen as control, by the PZ interindividual variability and by the small size of the cohorts in mainly retrospective studies. Large prospective studies remain to be done to investigate its possible role in thrombosis.

Database: Medline
11. Protein Z levels in pregnant Omani women: correlation with pregnancy outcome.

**Author(s):** Gowri, Vaidyanathan; Mathew, Mariam; Gravell, David; AlFalahi, Karima; Zakwani, Ibrahim; Ganguly, Shyam S; Pathare, Anil V

**Source:** Journal of thrombosis and thrombolysis; Nov 2011; vol. 32 (no. 4); p. 453-458

**Publication Date:** Nov 2011

**Publication Type(s):** Journal Article

**PubMedID:** 21837382

**Abstract:** Placental insufficiency resulting in fetal loss has been recognized in women with thrombophilic predisposition. Recent studies indicate that there is a high prevalence of protein Z (PZ) deficiency in patients with unexplained fetal loss. The objective of this study was to measure the PZ levels in pregnant Omani women in the first, second and third trimesters and correlate with the pregnancy outcome. The study enrolled 126 consecutive pregnant women after an informed consent prospectively. PZ was estimated in the first, second and third trimester in 15, 97 and 66 pregnant women respectively and they were followed for pregnancy outcomes including live birth, still birth, spontaneous abortion/induced abortion, maternal complications, fetal complications and health risks/complications in the newborn. The median PZ level (Mean ± SD) in the first, second and third trimester were 0.98 (1.07 ± 0.46), 1.3 (1.36 ± 0.61) and 1.44 (1.43 ± 0.69) (P < 0.05, Student's t-test, between first vs. second and first vs. third trimester). PZ deficiency defined as PZ level below 0.54 μg/ml (below 10th centile in the Omani population) was observed in 4 (4.7%) women, but interestingly all had a normal pregnancy outcome. Amongst the 43 subjects in whom paired PZ estimations were available, reducing PZ levels were observed from baseline values in 8 (33%) with normal pregnancy outcome; 5 (55%), with diabetes; 3 (50%) with hypertension and 2 (50%) with low birth weight respectively (P < 0.05, chi square test). PZ values increased progressively during the three trimesters of pregnancy. However, this increase is blunted in patients with abnormal pregnancy outcome like low birth weight babies or pregnancies associated hypertension or diabetes. Isolated PZ deficiency alone did not result in an abnormal outcome in this cohort of subjects.

**Database:** Medline
Protein-Z deficiency and/or protein Z polymorphisms in first trimester pregnancy complications

Author(s): Topalidou M.; Papadopoulos V.K.; Kartsios H.; Kokoviadou K.; Papadakis E.; Kioumi A.; Korantzis I.; Mpousiou Z.; Vakalopoulou S.; Garipidou V.; Chaloudis P.A.

Source: Blood; Nov 2011; vol. 118 (no. 21)

Publication Date: Nov 2011

Publication Type(s): Conference Abstract

Abstract: INTRODUCTION: Protein Z (PZ) is a vitamin K-dependent coagulation factor; it is a glycoprotein that inhibits activated factor Xa, acting as a co-factor to PZ-dependent protease inhibitor, enhancing its action approximately by 1000 times. PZ levels in normal individuals vary greatly, as a result of PZ gene polymorphisms. PZ deficiency has been involved in the pathogenesis of ischemic strokes and pregnancy complications. Gris et al [Blood 2002;99(7):2606-08] first described a possible role of PZ deficiency (PZ <= 1mg/L) in women with fetal loss between the beginning of the 10th and the end of the 15th week of gestation. In a recent meta-analysis [Sofi et al, Thrombosis and Haemostasis 2010;103(4):749-56] PZ deficiency was associated with increased risk of pre-eclampsia and fetal loss, as well as with increased risk of arterial and venous thrombotic events. MATERIALS-METHODS: We studied a total of 314 women, 70 women with three or more consecutive spontaneous abortions (group A), 145 women with less than 3 early spontaneous abortions (group B) and 99 control women with at least one normal pregnancy and negative history of a thrombotic complication (group C). All women were tested for congenital and acquired thrombophilia such as antithrombin, protein C and S levels, homocysteine levels, lupus anticoagulant (PTTLa), factor V Leiden mutation, prothrombin G20210A gene polymorphism and PZ levels. We also investigated protein Z polymorphism F79A in a subgroup of our patients. Measurements were made at least 3 months apart from a thrombotic event. Differences between groups were assessed with ANOVA and chi-squared tests for continuous and categorical variables respectively. RESULTS: Statistically significant difference was found in PZ levels between the three groups. Mean PZ level was 1.23mg/dL, 1.31mg/dL kappaalpha 1.61mg/dL (p<0.00001) in groups A, B, C respectively. Post-hoc Bonferroni analysis revealed a significant difference between groups A and C (p=0.0003) and between groups B and C (p=0.001). The percentage of PZ deficiency (95% confidence interval) was 40% (28%-52%), 38% (30%-46%) and 18% (11%-26%) respectively (p=0.001). Both group A (OddsRatio[OR]=3) and group B (OR=2.75) have a statistically greater PZ deficiency than control group C. The other parameters did not differ significantly between the three groups.

DISCUSSION/CONCLUSIONS: Spontaneous abortions are common in women especially in first trimester. Thrombophilia has a major role in pregnancy complications. In these women that one cannot find some of the well established thrombophilic factors, searching for other possible deficiencies is necessary. The role of PZ deficiency has been investigated thoroughly in the last decade with sometimes conflicting results. To the best of our knowledge, this is the first Greek study investigating the possible role of protein Z deficiency in women with early pregnancy losses. From our study it is evident that PZ deficiency is an independent risk factor for early pregnancy losses. From our study it seems that the other thrombophilic factors may play a minor role. A plausible pathophysiological explanation is the occurrence of microthrombi due to atherosclerotic lesions soon after the development of materno-placental circulation. The role of PZ gene polymorphisms in PZ levels and in thrombotic complications remains to be investigated further. According to preliminary results from a sub-group of our patients (Topalidou et al, Thrombosis Research 2009;124:24-27), the presence of the intron F79A polymorphism was associated with significantly lower PZ levels, but was unrelated to unexplained early pregnancy losses.

Database: EMBASE

**Author(s):** Sater, Mai S; Finan, Ramzi R; Al-Hammad, Salma A; Mohammed, Fatema A; Issa, Abdalla A; Almawi, Wassim Y

**Source:** American journal of reproductive immunology (New York, N.Y. : 1989); May 2011; vol. 65 (no. 5); p. 526-531

**Publication Date:** May 2011

**Publication Type(s):** Journal Article

**PubMedID:** 21087334

**Abstract:** PROBLEM: Protein Z (PZ) system is an anticoagulant pathway involved in the physiologic regulation of coagulation, and PZ deficiency reportedly enhances prothrombophilic mechanisms, including those implicated with idiopathic recurrent miscarriage (RSM). We investigate plasma anti-PZ IgM and IgG levels in RSM women and in multiparous control women.

**METHODS** Anti-PZ IgM and IgG levels were measured in 265 RSM women and 283 age-matched control women by ELISA.

**RESULTS** Elevated anti-PZ IgG (P < 0.001) and IgM (p < 0.001) titers were seen in patients. The areas under the curves for ROC curve for anti-PZ IgM (0.898 ± 0.044) and IgG (0.898 ± 0.042) demonstrated no variation in diagnostic capacity. Multivariate analysis confirmed the association of elevated anti-PZ IgM [adjusted odds ratio, aOR (95% CI) = 6.46 (2.44-17.11)] and IgG [aOR (95% CI) = 7.44 (2.54-21.79)] as independent predictors of RSM after adjusting for confounding covariates and demonstrated a clear gradation of increasing RSM risk associated with increased antibody titers.

**CONCLUSION** The presence of anti-PZ IgM and IgG antibodies are risk factors for RSM.

**Database:** Medline

14. Low levels of protein Z are associated with HELLP syndrome and its severity.

**Author(s):** Kaygusuz, Isik; Firatli-Tuglular, Tulin; Toptas, Tayfur; Ugurel, Vedat; Demir, Muzaffer

**Source:** Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis; Apr 2011; vol. 17 (no. 2); p. 214-219

**Publication Date:** Apr 2011

**Publication Type(s):** Comparative Study Journal Article

**PubMedID:** 20460354

**Abstract:** Protein Z (PZ) was found to be associated with pregnancy complications. There are no data implying an association between hemolysis (H), elevated liver enzymes (EL), and low platelet counts (LP) (HELLP) syndrome and changes in plasma levels of PZ. The aim of this study is to investigate whether HELLP syndrome is associated with plasma concentrations of PZ. Protein Z levels in 29 women with HELLP syndrome were compared with 29 healthy, nulliparous and 25 normal pregnant women. The median PZ levels in patients with HELLP syndrome were found to be significantly lower than those of pregnant women. No significant difference was found between HELLP and healthy groups. Protein Z levels correlated with platelet counts, lactate dehydrogenase (LDH), and aspartate aminotransferase (AST) levels in patients with HELLP syndrome. Median PZ level was higher in partial HELLP than in complete HELLP. We calculated 1330 ng/mL as a cutoff value for PZ level to discriminate HELLP syndrome from normal pregnancy. Low PZ levels are associated with the pathobiology of HELLP syndrome.

**Database:** Medline
15. Relationship of the protein Z intron F G79A and IL6 C634G gene polymorphisms with the risk of recurrent pregnancy loss in Egyptian women.

Author(s): El-Hamid, Samah Abd; El-Khayat, Waleed

Source: Journal of investigative medicine : the official publication of the American Federation for Clinical Research; Apr 2011; vol. 59 (no. 4); p. 655-660

Publication Date: Apr 2011

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

PubMedID: 21233768

Available at Journal of investigative medicine : the official publication of the American Federation for Clinical Research - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: PURPOSE To investigate the relationship between recurrent pregnancy loss and single nucleotide polymorphisms in the protein Z (PZ) intron F G79A and the promoter region of the IL6 C634G genes in Egyptian women. PROCEDURE Single nucleotide polymorphisms in the PZ intron F G79A gene and the promoter region of the IL6 C634G gene were studied in 70 Egyptian women; 40 patients and 30 healthy and parous volunteers using the polymerase chain reaction-restriction fragment length polymorphism technique. RESULTS Regarding the PZ intron F G79A polymorphism; a higher prevalence of the A allele in the controls (53.3%) compared with the cases (22.5%) was found, and the difference proved to be statistically significant (P = 0.008). As for the IL6 C634G polymorphism, the frequency of the G allele was higher in the controls (100%) than in the cases (95%), but the difference did not prove to be statistically significant (P = 0.503). A statistically significant difference between the prevalence of the IL6 C634G (95%) and the PZ intron F G79A (22.5%) was detected (P ≤ 0.001). CONCLUSION A statistically significant difference of the frequency of the A allele of the PZ intron F G79A polymorphism was found with a higher prevalence of the A allele among the controls compared with the patients, suggesting a lower risk of recurrent pregnancy loss among the studied patients, but the IL6 C634G polymorphism did not prove to have an equivalent effect.

Database: Medline
16. Protein Z levels and vascular thrombotic diseases: A meta-analysis

**Author(s):** Sofi F.; Cesari F.; Fedi S.; Abbate R.; Gensini G.F.; Broze G.J.

**Source:** European Journal of Cardiovascular Prevention and Rehabilitation; May 2010; vol. 17

**Publication Date:** May 2010

**Publication Type(s):** Conference Abstract

**Abstract:** Objective: The relationship between protein Z levels and thrombosis is controversial. We performed a systematic review and meta-analysis of all the available studies to assess the association between protein Z and vascular thrombotic diseases. Methods: We conducted an electronic literature search through MedLine, Embase, Google Scholar, Web of Science, The Cochrane Library, bibliographies of retrieved articles and abstracts of congresses up to May, 2009. Studies were included if they analysed protein Z levels in patients with vascular thrombotic diseases. Results: After the review process 28 case-control studies (33 cohort of patients) were included in the final analysis. These studies included 4,218 patients with thrombotic diseases as compared to 4,778 controls. The cumulative analysis for all the studies under a fixed-effects model showed that patients with low protein Z levels are at increased risk of occurring a thrombotic event (OR 1.87, 95%CI 1.62-2.15; p<0.00001). By subgrouping studies according to the different type of the disease, low protein Z levels were found to be a significant risk factor for arterial vascular diseases (OR 1.86, 95%CI 1.51-2.27; p<0.00001), and pregnancy complications (OR 3.42, 95%CI 2.51-4.66; p<0.00001) whereas only a limited significance for venous thromboembolic diseases (OR 1.28, 95%CI 1.00-1.65; p=0.05) was reported. Conclusion: This is the first meta-analysis that attempted to evaluate the role of protein Z on the occurrence of thrombotic events. The present results suggest, in an overall population of more than 4,000 patients, a possible implication for low levels of this coagulatory protein on the pathogenesis of thrombosis.

**Database:** EMBASE
17. The value of anti-protein Z as a marker of adverse obstetric history in systemic lupus erythematosus

Author(s): Taib S.; Bertolaccini M.L.; Murru V.; Hughes G.R.V.; Khamashta M.A.

Source: Lupus; Apr 2010; vol. 19 (no. 4); p. 536

Publication Date: Apr 2010

Publication Type(s): Conference Abstract

Abstract: Background: Protein Z deficiency has been associated with adverse obstetric history (AOH) and anti-prot Z have been found in women with pathological pregnancies. We studied the prevalence and clinical significance of anti-prot Z in a large cohort of SLE women. Patients and Methods: Of 75 women (mean age 46.5+/−11; mean disease duration 13.5+/−8.8), 32 had an adverse obstetric history (22 with a history of miscarriages (<10th week of gestation) and a total number of 55 events; 12 with a history of fetal death (310th week of gestation) and a total number of 17 deaths; 6 patients with a total number of 10 premature births at or before the 34th week of gestation). Only 20/32 fulfilled the 1999 Sapporo criteria for APS. Results: Anti-prot Z were present in 19% of the patients. The prevalence of anti-prot Z was not different between patients with AOH and those without (18.7% vs. 18.6%, OR 1.0 [95% CI 0.3-3.2], p=1.0). Levels of anti-prot Z were not significantly different between patients with AOH and those without (10.2+/−11.2 vs. 16.9+/−22.8, p=0.1). For further analysis, patients with AOH were subdivided in different subgroups, according to the event suffered. No differences were found in the prevalence and/or in the levels of anti-prot Z between patients with miscarriages and those without (13.6% vs. 20.7%, OR 0.6 [95% CI 0.1-2.4], p=0.7 and/or 9.2+/−8.7 vs. 16.1+/−21.6, p=0.1). Although anti-prot Z were more frequently found in patients with foetal death than in those without (33.3% vs. 15.8%), the difference did not reach statistical significance (OR 2.6 [95% CI 0.6-10.5], p=0.2). Levels of anti-prot Z were also not different between these 2 groups (13.5+/−14.6 vs. 14.2+/−19.7, p=0.9). No antibodies to protein Z were found in patients with history of prematurity. Conclusions: Anti-prot Z antibodies do not appear to be a risk marker for adverse obstetric outcome.

Database: EMBASE

Author(s): Erez, Offer; Romero, Roberto; Vaisbuch, Edi; Mazaki-Tovi, Shali; Kusanovic, Juan Pedro; Chaiworapongs, Tinnakorn; Than, Nandor Gabor; Gotsch, Francesca; Kim, Chong Jai; Mittal, Pooja; Edwin, Samuel; Pacora, Percy; Kim, Sun Kwon; Yeo, Lami; Mazor, Moshe; Hassan, Sonia S

Source: The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians; Aug 2009; vol. 22 (no. 8); p. 662-671

Publication Date: Aug 2009

Publication Type(s): Research Support, N.i.h., Intramural Journal Article

PubMedID: 19591071

Abstract: OBJECTIVE Low maternal plasma protein Z (PZ) concentrations were reported in patients with pre-eclampsia (PE), a small for gestational age (SGA) neonate, and a fetal demise (FD). Anti-protein Z antibodies (APZ-AB) have been proposed as a possible underlying mechanism leading to low plasma PZ concentrations. The objective of this study was to determine the maternal plasma concentration of APZ-AB in women with a normal pregnancy, and patients with PE, an SGA neonate or a FD. STUDY DESIGN A cross-sectional study included women in the following groups: (1) non-pregnant women (n = 45); and pregnant women with: (2) normal pregnancies (n = 70); (3) PE (n = 123); (4) SGA neonates (n = 51); and (5) a FD (n = 51). Plasma concentrations of anti-protein Z IgM and IgG antibodies were measured by ELISA. Elevated APZ-AB was defined as >75th, 90th and 95th percentile of the normal pregnancy group. Non-parametric statistics were used for analyses.

RESULTS (1) Patients with an SGA neonate had a higher median maternal plasma IgG APZ-AB concentration than women with normal pregnancies (p < 0.001), and patients with PE (p 90th percentile was higher in the SGA group than in the PE group (p = 0.01). (3) Patients with PE maternal plasma IgM APZ-AB concentration >90th percentile had a higher rate of villous thrombosis (p = 0.03) and persistent muscularization of basal plate arteries (p = 0.01) than those with IgM APZ-AB concentration 90th percentile had a higher rate of umbilical phlebitis and arteritis than those with IgM APZ-AB concentration 90th percentile was associated with vascular placental lesions in patients with PE, but not in those with an SGA neonate, suggesting that in a subset of patients, these antibodies can be associated with abnormal placentation and pregnancy complications.

Database: Medline
19. Low protein Z levels, but not the intron F G79A polymorphism, are associated with unexplained pregnancy loss.

**Author(s):** Topalidou, Maria; Effraimidou, Smaragda; Farmakiotis, Dimitrios; Papadakis, Emmanuel; Papaioannou, Georgia; Korantzis, Ioannis; Garipidou, Vassilia

**Source:** Thrombosis research; May 2009; vol. 124 (no. 1); p. 24-27

**Publication Date:** May 2009

**Publication Type(s):** Journal Article

**PubMedID:** 19026439

**Abstract:**

**INTRODUCTION**
The present case-control study was designed in order to investigate the association between plasma protein Z (PZ) levels, the intron F G79A polymorphism and unexplained pregnancy loss.

**MATERIALS AND METHODS**
51 women with at least two consecutive or three non-consecutive fetal losses between the 8th and 12th week of gestation and 47 apparently healthy parous women of reproductive age with no history of pregnancy loss (controls) were enrolled. Allele frequencies of the PZ intron F G79A polymorphism and PZ levels were measured.

**RESULTS**
PZ levels (mg/L) were significantly lower in cases (mean +/- S.D. 1.28 +/- 0.56) than controls (1.97 +/- 0.76, p < 0.001) and in carriers of the A allele (1.46 +/- 0.62), compared to GG homozygous subjects (1.72 +/- 0.81, p = 0.044). A higher proportion of cases (41.2%) were PZ-deficient (<1 mg/L), compared to controls (10.6%, p = 0.001). No significant difference in the frequency of at least one A allele carriers was observed between cases (39.2%) and controls (40.4%).

**CONCLUSION(S)**
It is possible that low PZ levels are a novel risk factor for unexplained recurrent miscarriage or fetal death. The presence of the F 79A allele is associated with significantly lower PZ levels, but, in the present study, was unrelated to unexplained early pregnancy loss.

**Database:** Medline

20. Protein Z g-42a variant and the risk of pregnancy-related venous thromboembolism in a cohort of Italian patients.

**Author(s):** Grandone, Elvira; Favuzzi, Giovanni; De Stefano, Valerio; Chinni, Elena; Rossi, Elena; Cappucci, Filomena; Margaglione, Maurizio

**Source:** Thrombosis research; Apr 2009; vol. 123 (no. 6); p. 848-850

**Publication Date:** Apr 2009

**Publication Type(s):** Journal Article

**PubMedID:** 19185907

**Database:** Medline

**Author(s):** Sailer, Thomas; Vormittag, Rainer; Koder, Silvia; Quehenberger, Peter; Kaider, Alexandra; Pabinger, Ingrid

**Source:** Thrombosis Research; 2008; vol. 122 (no. 2); p. 153-160

**Publication Date:** 2008

**PubMed ID:** 18031797

**Abstract:**

**INTRODUCTION**

Protein Z serves as cofactor for the inactivation of factor Xa by the plasma protein Z-dependent protease inhibitor. Deficiency of protein Z was reported to exhibit a clinical manifestation like lupus anticoagulant characterised by thrombosis and fetal loss. As anti-protein Z antibodies may be associated with low protein Z levels, we hypothesised that anti-protein Z antibodies might play a role in lupus anticoagulant (LA).

**MATERIALS AND METHODS**

Anti-protein Z antibodies were measured by commercially available ELISA in 102 LA-patients (69 with and 33 without thrombosis) and 33 healthy volunteers.

**RESULTS**

Elevated anti-protein Z IgG and/or IgM, IgG and IgM antibody levels were more prevalent among LA-patients (62%, 35%, 45%) than among controls (50%, 25%, 25%), but the difference was only statistically significant for the IgM subtype (p=0.037). Anti-protein Z IgG (odds ratio [OR] 0.77, 95% confidence interval [CI] 0.33-1.82) and IgM (OR 0.82, CI 0.35-1.88) antibody levels in the highest quartile of controls did not indicate an increased risk for thrombosis among LA-patients. Anti-protein Z IgG (OR 2.0, CI 0.5-7.6) and IgM (OR 1.8, CI 0.5-6.6) antibody levels in the highest quartile of controls were more prevalent in women with pregnancy loss than in those with normal pregnancy, but the difference was not statistically significant.

**CONCLUSION**

Our data indicate that anti-protein Z antibodies are not associated with thrombosis in LA. However, women with LA and pregnancy loss show a tendency towards elevated anti-protein Z antibody levels.

**Database:** Medline

**Author(s):** Dossenbach-Glaninger, Astrid; van Trotsenburg, Michael; Helmer, Hanns; Oberkanins, Christian; Hopmeier, Pierre

**Source:** Fertility and sterility; Oct 2008; vol. 90 (no. 4); p. 1155-1160

**Publication Date:** Oct 2008

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 18177644

**Abstract:**

OBJECTIVE: To investigate the association of the common protein Z (PZ) intron F G79A gene polymorphism with recurrent early pregnancy loss (RPL) and its gene-gene interaction with known thrombophilic risk factors for RPL.

DESIGN: Case control study.

SETTING: University clinic.

PATIENT(S): We enrolled 49 women with a history of two consecutive or three to six nonconsecutive pregnancy losses between the 8th and 12th weeks of gestation and 48 age-matched parous controls without a history of pregnancy complications.

INTERVENTION(S): None.

MAIN OUTCOME MEASURE(S): Allele frequencies of the PZ intron F G79A polymorphism and its gene-gene interaction with known risk factors for RPL.

RESULT(S): Fourteen case subjects (28.6%) and 24 control subjects (50.0%) carried at least one A allele. This was associated with a significant reduction of the relative risk for recurrent pregnancy loss (odds ratio [OR] 0.4, 95% confidence interval [CI] 0.2-0.9; adjusted OR 0.3, 95% CI 0.1-0.8). Coexistence of any thrombophilic risk factor studied with the 79A allele resulted in a clear reduction of the primal relative risk for recurrent pregnancy loss.

CONCLUSION(S): The isolated presence of the PZ intron F 79A allele as well as the combination with known thrombophilic risk factors was protective against RPL between the 8th and 12th weeks of gestation.

**Database:** Medline
23. Pyelonephritis during pregnancy: a cause for an acquired deficiency of protein Z.

**Author(s):** Nien, Jyh Kae; Romero, Roberto; Hoppensteadt, Debra; Erez, Offer; Espinoza, Jimmy; Soto, Eleazar; Kusanovic, Juan Pedro; Gotsch, Francesca; Kim, Chong Jai; Mittal, Pooja; Fareed, Jawed; Santolaya, Joaquin; Chaiworapongs, Tinnakorn; Edwin, Samuel; Pineles, Beth; Hassan, Sonia

**Source:** The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians; Sep 2008; vol. 21 (no. 9); p. 629-637

**Publication Date:** Sep 2008

**Publication Type(s):** Journal Article

**PubMedID:** 18828054


**Abstract:**

**OBJECTIVE**

Pyelonephritis has a more severe course during pregnancy than in the non-pregnant state. This has been attributed to the increased susceptibility of pregnant women to microbial products. An acquired protein Z deficiency has been reported when there is excessive thrombin activity. The aim of this study was to determine whether pyelonephritis during pregnancy is associated with changes in maternal plasma protein Z concentrations.

**STUDY DESIGN**

A cross-sectional study was conducted to compare plasma protein Z concentrations between normal pregnant women (N = 71) and pregnant women with pyelonephritis (N = 42). Protein Z concentrations were measured by enzyme-linked immunosorbent assay. Parametric and non-parametric statistics were used for analysis.

**RESULT**

Patients with pyelonephritis had a significantly lower median plasma concentration of protein Z than did patients with normal pregnancies (median 2.14 microg/mL (0.4-3.4) vs. median 2.36 microg/mL (1.09-3.36); p = 0.03). There was no difference in the median plasma concentration of anti-protein Z antibodies between patients with pyelonephritis and those with normal pregnancies.

**CONCLUSION**

The median maternal plasma protein Z concentration was significantly lower in patients with pyelonephritis during pregnancy than in patients with normal pregnancies.

**Database:** Medline

---

24. An unreported mutation within protein Z gene is associated with very low protein levels in women with fetal loss.

**Author(s):** Grandone, Elvira; Colaizzo, Donatella; Cappucci, Filomena; D'Ambrosio, Rosa Lucia; Vecchione, Gennaro; Margaglione, Maurizio

**Source:** Fertility and sterility; Sep 2008; vol. 90 (no. 3); p. 864-865

**Publication Date:** Sep 2008

**Publication Type(s):** Journal Article

**PubMedID:** 18462727

**Abstract:**

Gene variant intron C G-42A of protein Z is significantly associated with the occurrence of fetal loss. A previously unreported sporadic missense mutation within exon 8 is described in a patient with very low protein Z levels.

**Database:** Medline
25. **Preeclampsia is associated with low concentrations of protein Z.**

**Author(s):** Erez, Offer; Hoppensteadt, Debra; Romero, Roberto; Espinoza, Jimmy; Goncalves, Luis; Nien, Jyh Kae; Kusanovic, Juan Pedro; Fareed, Jawed; Gotsch, Francesca; Pineles, Beth; Chaiworapongsa, Tinnakorn

**Source:** The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians; Sep 2007; vol. 20 (no. 9); p. 661-667

**Publication Date:** Sep 2007

**Publication Type(s):** Comparative Study Research Support, N.i.h., Intramural Journal Article

**PubMedID:** 17701666

Available at The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:** **OBJECTIVE** Protein Z, a vitamin K-dependent plasma protein, has an important role in the regulation of the coagulation cascade. Protein Z deficiency has been associated with unexplained pregnancy loss and adverse pregnancy outcome in patients with thrombophilia. This study was conducted to determine if preeclampsia (PE), small for gestational age (SGA), and fetal demise are associated with changes in maternal plasma concentrations of protein Z.

**STUDY DESIGN** This cross-sectional study included normal pregnant women (N = 71), patients with PE (N = 130), patients who delivered an SGA neonate (N = 58), and patients with fetal demise (N = 58). Maternal plasma protein Z concentrations were measured by a sensitive and specific immunoassay. Protein Z deficiency was defined as maternal plasma concentrations \(<or=5th\) percentile of the normal pregnancy group (\(<or=1.59\) microg/mL). Non-parametric statistics were used for analysis.

**RESULTS** (1) Patients with PE had a lower median plasma concentration of protein Z than normal pregnant women (PE: median 1.6 microg/mL, range 0.2-3.3 microg/mL vs. normal pregnancy: median 2.4 microg/mL, range 1.1-3.4 microg/mL; p  0.05); and (3) women in the PE and fetal demise groups had significantly higher rates of protein Z deficiency than those with normal pregnancy outcome.

**CONCLUSIONS** (1) PE, but not SGA or fetal demise, is associated with a significantly lower maternal median plasma concentration of protein Z than normal pregnancy, and (2) a high rate of protein Z deficiency is observed in patients with PE and fetal demise.

**Database:** Medline
26. Plasma protein Z concentrations in pregnant women with idiopathic intrauterine bleeding and in women with spontaneous preterm labor.

Author(s): Kusanovic, Juan Pedro; Espinoza, Jimmy; Romero, Roberto; Hoppensteadt, Debra; Nien, Jyh Kae; Kim, Chong Jai; Erez, Offer; Soto, Eleazar; Fareed, Jawed; Edwin, Sam; Chaiwerapongsa, Tinnakorn; Than, Nador G; Yoon, Bo Hyun; Gomez, Ricardo; Papp, Zoltan; Hassan, Sonia S

Source: The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians; Jun 2007; vol. 20 (no. 6); p. 453-463

Publication Date: Jun 2007
Publication Type(s): Research Support, N.i.h., Intramural Journal Article
PubMedID: 17674255

Available at The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: OBJECTIVES: Preterm parturition has been associated with decidual vascular disorders and excessive thrombin generation. The objective of this study was to examine maternal plasma concentrations of protein Z in normal pregnancies, as well as in those presenting with spontaneous preterm labor (PTL) and intrauterine bleeding during pregnancy. STUDY DESIGN: A cross-sectional study was designed to include patients with preterm labor and intact membranes and those with idiopathic intrauterine bleeding during pregnancy. Protein Z plasma concentrations were measured in the following groups: (1) normal pregnant women (n = 71); (2) patients at term with (n = 67) and without labor (n = 88); (3) patients with spontaneous PTL before 34 weeks who were classified into: (a) PTL with intra-amniotic infection/inflammation (IAI; n = 35), (b) PTL without IAI (n = 54), and (c) patients with PTL who delivered at term (n = 49); and (4) patients with idiopathic intrauterine bleeding in the second and third trimester who were divided into: (a) subsequent spontaneous PTL and delivery, and (b) term delivery. Maternal plasma protein Z concentration was measured by a specific and sensitive immunoassay. Moreover, the amniotic fluid concentration of protein Z was determined in a subset of patients with preterm labor (n = 30). RESULTS: (1) There was no correlation between maternal plasma protein Z concentration and gestational age in normal pregnant women. (2) The mean maternal plasma concentration of protein Z was significantly lower in women during spontaneous labor at term than in those not in labor (mean 2.15 microg/mL (95% CI 2.01-2.29) vs. mean 2.45+/-0.52 microg/mL (95% CI 2.34-2.56), respectively; p = 0.001). (3) Women with PTL without IAI who delivered preterm had a significantly lower mean protein Z concentration than normal pregnant women (mean 2.12 mug/mL (95% CI 1.98-2.26) vs. mean 2.39 microg/mL (95% CI 2.28-2.5); p = 0.008). (4) Of interest, PTL with IAI was not associated with lower plasma concentrations of protein Z, nor were those with PTL who delivered at term (p > 0.05 for each). (5) No differences were found in the maternal plasma concentrations of anti-protein Z antibodies between normal pregnancies and those with spontaneous PTL. (6) Patients with idiopathic intrauterine bleeding who had spontaneous PTL and delivery had a significantly lower mean plasma protein Z concentration than those who delivered at term (mean 1.24 microg/mL (95% CI 1.08-1.4) vs. mean 1.49+/-0.47 microg/mL (95% CI 1.33-1.65), respectively; p = 0.03). (7) Amniotic fluid was found to contain immunoreactive protein Z. CONCLUSIONS: (1) Patients with PTL leading to preterm delivery in the absence of IAI had a significantly lower plasma concentration of protein Z than those with normal pregnancies. (2) Patients with idiopathic intrauterine bleeding and subsequently spontaneous PTL and delivery had a significantly lower plasma concentration of protein Z than those with idiopathic intrauterine bleeding who delivered at term. (3) Protein Z was present in the amniotic fluid of patients with PTL. Collectively, these observations suggest that a subgroup of
patients with PTL have a hemostatic disorder that involves bleeding/thrombosis as a mechanism of disease.

Database: Medline

27. Protein Z in patients with pregnancy complications.

Author(s): Bretelle, Florence; Arnoux, Dominique; Shojai, Raha; D’Ercole, Claude; Sampol, José; Dignat, Françoise; Camoin-Jau, Laurence

Source: American journal of obstetrics and gynecology; Nov 2005; vol. 193 (no. 5); p. 1698-1702

Publication Date: Nov 2005

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

PubMedID: 16260213

Abstract: OBJECTIVE: This study was undertaken to evaluate the association between protein Z concentration and pregnancy complications. STUDY DESIGN: A prospective case-control study was conducted over a 2-year period to evaluate the prevalence of protein Z deficiency in pregnancy complications. Protein Z levels were measured at the time of diagnosis of complications such as preeclampsia, intrauterine growth restriction, and intrauterine fetal demise. Protein Z deficiency was defined as a plasma level below 1.2 mg/L. In addition to patients presenting with pregnancy complications, healthy age-matched nonpregnant and pregnant women were invited to participate. RESULTS: A total of 145 women were included in the study: 50 nonpregnant women, 34 healthy pregnant women, 29 women with preeclampsia, 25 women presented with intrauterine growth restriction, and 7 women with intrauterine fetal demise. The median protein Z level was similar in healthy pregnant and nonpregnant women (1.63 [0.47-3.1] mg/L and 1.69 [0.7-3] mg/L, respectively). Three women with normal pregnancies had a low protein Z level (8.8%), compared with 8 patients presenting with intrauterine growth restriction (33.3%) and 8 patients with intrauterine fetal demise (50%). Compared with normal pregnancy, the frequency of decreased protein Z was significantly higher in cases of intrauterine growth restriction and in intrauterine fetal demise (relative risk [RR] 1.96, 95% CI 1.16-3.32; P = .041 and RR 3.36, 95% CI 1.65-6.8; P = .0031, respectively), but not in preeclampsia (RR 1.6, 95% CI 0.9-2.8; P = .23). Placenta histologic examination revealed vascular lesions in 50% of patients with protein Z deficiency and in 33% of patients with normal levels of protein Z (RR 0.84; 95% CI 0.6-1.2). CONCLUSION: Protein Z deficiency is associated with late fetal demise and intrauterine growth restriction. The pathophysiologic role of protein Z deficiency, either congenital or caused by the presence of specific antibodies remains unclear and should be further investigated.

Database: Medline

Author(s): Dörner, T; Hoppe, B; Salama, A; Pruss, A; Kiesewetter, H
Source: Clinical and experimental medicine; Jul 2005; vol. 5 (no. 2); p. 50-54
Publication Date: Jul 2005
Publication Type(s): Journal Article Review
PubMedID: 16096853

Abstract: Protein Z (PZ) is a vitamin K-dependent plasma protein that serves as a cofactor for the inactivation of factor Xa. A number of investigators found low PZ levels in patients with haemorrhagic as well as thromboembolic diseases, although there is no clear evidence of a pathogenic link between PZ deficiency and these clinical disorders. Nevertheless, low PZ levels have been found in association with early fetal losses, especially those occurring before the 15th week of gestation and in patients with detectable antiphospholipid and anti-PZ antibodies. The current diagnostic relevance and therapeutic consequences of these parameters will be discussed.

Database: Medline

29. Inherited thrombophilias and adverse pregnancy outcome: screening and management.

Author(s): Paidas, Michael J; Ku, De-Hui W; Langhoff-Roos, Jens; Arkel, Yale S
Source: Seminars in perinatology; Jun 2005; vol. 29 (no. 3); p. 150-163
Publication Date: Jun 2005
Publication Type(s): Journal Article Review
PubMedID: 16114578

Abstract: Inherited thrombophilias are a heterogenous group of conditions which have been implicated in a variety of pregnancy complications. Evidence is mounting that implicates these inherited disorders in a range of pregnancy outcomes, including recurrent miscarriage, late fetal loss, preeclampsia, abruptio placentae, and intrauterine growth restriction. The most commonly identified inherited thrombophilias consist of Factor V Leiden and the prothrombin gene mutation G20210A. Rarer inherited thrombophilic conditions include deficiencies of protein S, C and antithrombin. More recently, deficiency of protein Z has been linked to pregnancy complications, including preterm delivery. Clinical manifestations often are associated with the presence of more than one inherited thrombophilia, consistent with their multigenic nature. Some, but not all, studies investigating the use of heparin to prevent adverse pregnancy outcome have demonstrated a benefit. However, an adequate randomized trial is required to definitively determine whether heparin anticoagulation is the best prevention option in patients who harbor one or more inherited thrombophilias and are at risk for adverse pregnancy outcome. This review will summarize the association of thrombophilic conditions and obstetrical complications.

Database: Medline
30. Protein Z in normal pregnancy.

Author(s): Quack Loetscher, Katharina C; Stiller, Ruth; Roos, Malgorzata; Zimmermann, Roland

Source: Thrombosis and haemostasis; Apr 2005; vol. 93 (no. 4); p. 706-709

Publication Date: Apr 2005

Publication Type(s): Journal Article

PubMedID: 15841316

Abstract: Changes in the coagulation and fibrinolytic systems during pregnancy lead to a higher risk of thromboembolism. These changes include the increase of many clotting factors, as well as a significant fall in activity of fibrinolytic proteins, such as protein C. Protein Z is a vitamin-K-dependent plasma glycoprotein and inhibits the activation of factor X by serving as a cofactor to a plasma proteinase inhibitor. Protein Z deficiency has recently been reported in women with unexplained early fetal losses, and antibodies to protein Z can contribute to adverse pregnancy outcomes. The aim of this study was to determine the range of protein Z in normal pregnancies at different gestational weeks in a cross-sectional and a longitudinal setting. In the longitudinal study we found a 20% increase (p=0.006) of protein Z from first trimester to delivery and a 30% decrease (p<0.0001) 6 to 12 weeks after delivery. In the cross-sectional study these findings were reproducible. In summary, our data show a progressive increase in protein Z levels with gestational age in normal pregnancies and a return to normal levels around 6 to 12 weeks postpartum. The normal increase of protein Z during pregnancy may balance the increase of clotting factors to protect pregnant women from thrombosis.

Database: Medline

31. Protein Z, protein S levels are lower in patients with thrombophilia and subsequent pregnancy complications.

Author(s): Paidas, M J; Ku, D-H W; Lee, M-J; Manish, S; Thurston, A; Lockwood, C J; Arkel, Y S

Source: Journal of thrombosis and haemostasis : JTH; Mar 2005; vol. 3 (no. 3); p. 497-501

Publication Date: Mar 2005

Publication Type(s): Research Support, Non-u.s. Gov't Research Support, N.i.h., Extramural Journal Article Research Support, U.s. Gov't, P.h.s.

PubMedID: 15748239

Available at Journal of thrombosis and haemostasis : JTH - from Wiley Online Library Free Content - NHS

Available at Journal of thrombosis and haemostasis : JTH - from IngentaConnect - Open Access

Abstract: OBJECTIVE We posit that low levels of protein S (PS) and protein Z (PZ) contribute to adverse pregnancy outcome (APO). PATIENTS We evaluated 103 women with subsequent normal pregnancy outcome (NPO), 106 women with APO, and 20 women with thrombophilia (TP). METHODS We compared first trimester (1st TRI) PZ levels in 103 women with NPO, 106 women with APO, and in 20 women with TP. We compared plasma levels of PZ and free PS antigen during the second (2nd TRI) and third trimesters (3rd TRI) of pregnancy in 51 women with APO and 51 matched women with NPO. RESULTS The mean 1st TRI PZ level was significantly lower among patients with APO, compared to pregnant controls (1.81 +/- 0.7 vs. 2.21 +/- 0.8 microg mL(-1), respectively, P < 0.001). Of patients with known TP, those with APO had a tendency for lower mean PZ levels compared to those TP women with NPO (1.5 +/- 0.6 vs. 2.3 +/- 0.9 microg mL(-1), respectively, P < 0.0631). There was a significant decrease in the PZ levels in patients with APO compared to NPO (2nd TRI 1.5 +/- 0.4 vs. 2.0 +/- 0.5 microg mL(-1), P < 0.0001; and 3rd TRI 1.6 +/- 0.5 vs. 1.9 +/- 0.5 microg mL(-1), P < 0.0002). Protein S levels were significantly lower in the 2nd and
3rd TRIs among patients with APO compared to patients with NPO (2nd TRI 34.4 +/- 11.8% vs. 38.9 +/- 10.3%, P < 0.05, respectively; and 3rd TRI 27.5 +/- 8.4 vs. 31.2 +/- 7.4, P < 0.025, respectively). CONCLUSIONS We posit that decreased PZ and PS levels are additional risk factors for APO.

**Database:** Medline

### 32. Screening and management of inherited thrombophilias in the setting of adverse pregnancy outcome.

**Author(s):** Paidas, Michael J; Ku, De-Hui W; Arkel, Yale S

**Source:** Clinics in perinatology; Dec 2004; vol. 31 (no. 4); p. 783-806

**Publication Date:** Dec 2004

**Publication Type(s):** Journal Article Review

**PubMedID:** 15519428

**Abstract:** Inherited thrombophilic conditions are associated with adverse pregnancy outcomes, including severe pre-eclampsia, fetal loss, abruptio placenta, and intrauterine growth restriction. Although the prevalence of these complications is approximately 8% in the general population, their presence is associated with a significantly increased recurrence risk. Thrombophilic conditions most strongly associated with adverse pregnancy outcome include factor V Leiden, prothrombin gene mutation, and deficiencies of protein S, protein C, and antithrombin. Other thrombophilic conditions, such as protein Z deficiency, also appear to be associated with an increased risk of pregnancy complications. Antenatal administration of heparin to prevent pregnancy complications has shown promise in small studies, but a randomized, placebo-controlled trial is necessary to determine whether heparin administration is beneficial in preventing adverse pregnancy outcome.

**Database:** Medline

### 33. Protein Z levels and unexplained fetal losses.

**Author(s):** Grandone, Elvira; Colaizzo, Donatella; Cappucci, Filomena; Cocomazzi, Nicola; Margaglione, Maurizio

**Source:** Fertility and sterility; Oct 2004; vol. 82 (no. 4); p. 982-983

**Publication Date:** Oct 2004

**Publication Type(s):** Journal Article

**PubMedID:** 15482789

**Abstract:** We evaluated protein Z plasma levels in a group of women with fetal losses (n = 124) and compared them with those in a group of women (n = 60) with uneventful pregnancies. We found that protein Z deficiency is not associated with otherwise unexplained fetal losses.

**Database:** Medline
34. Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder.

Author(s): Gris, Jean-Christophe; Mercier, Eric; Quéré, Isabelle; Lavigne-Lissalde, Géraldine; Cochery-Nouvellon, Eva; Hoffet, Médoc; Ripart-Neveu, Sylvie; Tailland, Marie-Laure; Dauzat, Michel; Marès, Pierre

Source: Blood; May 2004; vol. 103 (no. 10); p. 3695-3699

Publication Date: May 2004

Publication Type(s): Research Support, Non-u.s. Gov't Comparative Study Randomized Controlled Trial Clinical Trial Journal Article

PubMedID: 14739212

Available at Blood - from HighWire - Free Full Text

Abstract:The prospective evaluation of the effect of thromboprophylaxis in women with one unexplained pregnancy loss from the 10th week of amenorrhea was performed. A total of 160 patients with heterozygous factor V Leiden mutation, prothrombin G20210A mutation, or protein S deficiency were given 5 mg folic acid daily before conception, to be continued during pregnancy, and low-dose aspirin 100 mg daily or low-molecular-weight heparin enoxaparin 40 mg was taken from the 8th week. Twenty-three of the 80 patients treated with low-dose aspirin and 69 of the 80 patients treated with enoxaparin had a healthy live birth (odds ratio [OR], 15.5; 95% confidence interval [CI], 7-34, P <.0001). Enoxaparin was superior to low-dose aspirin in each subgroup defined according to the underlying constitutional thrombophilic disorder. An associated protein Z deficiency and/or positive antiprotein Z antibodies were associated with poorer outcomes. The neonate weight was higher in the women successfully treated with enoxaparin, and neonates small for gestational age were more frequent in patients treated with low-dose aspirin. No significant side effects of the treatments could be evidenced in patients or newborns. As there is no argument to prove that low-dose aspirin may have been deleterious, these results support enoxaparin use during such at-risk pregnancies.

Database: Medline
35. Anti-protein Z antibodies in women with pathologic pregnancies.

Author(s): Gris, Jean-Christophe; Amadio, Cécile; Mercier, Eric; Lavigne-Lissalde, Géraldine; Déchaud, Hervé; Hoffet, Médéric; Quéré, Isabelle; Amiral, Jean; Dauzat, Michel; Marès, Pierre

Source: Blood; Jun 2003; vol. 101 (no. 12); p. 4850-4852

Publication Date: Jun 2003
Publication Type(s): Journal Article
PubMedID: 12623836

Abstract: Protein Z deficiencies have recently been described in women with unexplained early fetal loss. Using a new, specifically elaborated, commercially available enzyme-linked immunosorbent assay (ELISA), we performed a case-control study on anti-protein Z immunoglobulin G (IgG) and IgM antibodies in 191 nonthrombotic, nonthrombophilic women with consecutive pathologic pregnancies. Levels of anti-protein Z antibodies were categorized in 3 strata (percentiles 1 through 74, 75 through 97, 98 through 100 among controls). The 2 upper levels of IgG and IgM anti-protein Z antibodies were associated with the risk of unexplained recurrent embryo loss or fetal death independently from habitual antiphospholipid/anticofactor antibodies, and a dose-effect relationship between antibody levels and the clinical risks was evidenced. In women, enhanced immune-complex formation with protein Z may play a role in unexplained embryo losses and, from the 10th week of gestation, may favor hypercoagulability in the maternal placenta side.

Database: Medline


Author(s): Gris, Jean-Christophe; Quéré, Isabelle; Dechaud, Hervé; Mercier, Eric; Pinçon, Caroline; Hoffet, Médéric; Vasse, Marc; Marès, Pierre

Source: Blood; Apr 2002; vol. 99 (no. 7); p. 2606-2608

Publication Date: Apr 2002
Publication Type(s): Journal Article
PubMedID: 11895801

Abstract: The protein Z-protein Z-dependent inhibitor complex is a factor Xa inhibitor. Protein Z deficiencies have recently been described in patients with ischemic stroke. As placenta infarction leads to poor pregnancy outcome, we studied protein Z plasma concentrations in nonthrombotic, nonthrombophilic consecutive patients with unexplained pregnancy wastage. A significant amount of protein Z deficiencies was only found in the early fetal loss group (< 1 mg/L; 44 of 200, P < 10(-4)) and mainly in the case of fetal demise between the beginning of the 10th and the end of the 15th week of gestation (odds ratio, 6.7 [3.1-14.8], P < 10(-3)). These deficiencies were not due to partial vitamin K1 deficiency, and at least some of them were constitutional ones. In women, protein Z deficiency may induce an enhanced risk of severe placental insufficiency soon after the connection of maternal and fetal circulations.

Database: Medline
<table>
<thead>
<tr>
<th>#</th>
<th>Database</th>
<th>Search term</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Medline</td>
<td>(&quot;protein Z&quot; ADJ2 deficien*).ti,ab</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>Medline</td>
<td>(&quot;protein Z&quot;).ti,ab</td>
<td>435</td>
</tr>
<tr>
<td>3</td>
<td>Medline</td>
<td>(1 OR 2)</td>
<td>435</td>
</tr>
<tr>
<td>4</td>
<td>Medline</td>
<td>(pregnan*).ti,ab</td>
<td>442767</td>
</tr>
<tr>
<td>5</td>
<td>Medline</td>
<td>exp PREGNANCY/</td>
<td>832885</td>
</tr>
<tr>
<td>6</td>
<td>Medline</td>
<td>exp &quot;PREGNANCY COMPLICATIONS&quot;/</td>
<td>397893</td>
</tr>
<tr>
<td>7</td>
<td>Medline</td>
<td>exp &quot;PREGNANCY OUTCOME&quot;/</td>
<td>50278</td>
</tr>
<tr>
<td>8</td>
<td>Medline</td>
<td>(4 OR 5 OR 6 OR 7)</td>
<td>955177</td>
</tr>
<tr>
<td>9</td>
<td>Medline</td>
<td>(3 AND 8)</td>
<td>47</td>
</tr>
<tr>
<td>10</td>
<td>EMBASE</td>
<td>exp &quot;PROTEIN DEFICIENCY&quot;/</td>
<td>28598</td>
</tr>
<tr>
<td>11</td>
<td>EMBASE</td>
<td>(&quot;protein z &quot;).ti,ab</td>
<td>528</td>
</tr>
<tr>
<td>12</td>
<td>EMBASE</td>
<td>(&quot;protein pz &quot;).ti,ab</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>EMBASE</td>
<td>(11 OR 12)</td>
<td>548</td>
</tr>
<tr>
<td>14</td>
<td>EMBASE</td>
<td>(10 AND 13)</td>
<td>50</td>
</tr>
<tr>
<td>15</td>
<td>EMBASE</td>
<td>(&quot;protein Z&quot; ADJ2 deficien*).ti,ab</td>
<td>64</td>
</tr>
<tr>
<td>16</td>
<td>EMBASE</td>
<td>(14 OR 15)</td>
<td>82</td>
</tr>
<tr>
<td>17</td>
<td>EMBASE</td>
<td>(PZD).ti,ab</td>
<td>87</td>
</tr>
<tr>
<td>18</td>
<td>EMBASE</td>
<td>(16 OR 17)</td>
<td>168</td>
</tr>
<tr>
<td>19</td>
<td>EMBASE</td>
<td>(pregnan*).ti,ab</td>
<td>577419</td>
</tr>
<tr>
<td></td>
<td>Database</td>
<td>Query</td>
<td>Count</td>
</tr>
<tr>
<td>---</td>
<td>----------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>20</td>
<td>EMBASE</td>
<td>exp PREGNANCY/</td>
<td>694145</td>
</tr>
<tr>
<td>21</td>
<td>EMBASE</td>
<td>exp &quot;PREGNANCY COMPLICATION&quot;/</td>
<td>126577</td>
</tr>
<tr>
<td>22</td>
<td>EMBASE</td>
<td>exp &quot;PREGNANCY OUTCOME&quot;/</td>
<td>48365</td>
</tr>
<tr>
<td>23</td>
<td>EMBASE</td>
<td>(19 OR 20 OR 21 OR 22)</td>
<td>919554</td>
</tr>
<tr>
<td>24</td>
<td>EMBASE</td>
<td>(18 AND 23)</td>
<td>63</td>
</tr>
<tr>
<td>25</td>
<td>EMBASE</td>
<td>(low ADJ2 &quot;protein z&quot;).ti,ab</td>
<td>31</td>
</tr>
<tr>
<td>26</td>
<td>EMBASE</td>
<td>(low ADJ2 &quot;protein pz&quot;).ti,ab</td>
<td>0</td>
</tr>
<tr>
<td>27</td>
<td>EMBASE</td>
<td>(25 OR 26)</td>
<td>31</td>
</tr>
<tr>
<td>28</td>
<td>EMBASE</td>
<td>(23 AND 27)</td>
<td>7</td>
</tr>
</tbody>
</table>