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## Beta-2-glycoprotein I and urinary trypsin inhibitor levels in the plasma of pregnant and postpartum women

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### KEYWORDS

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coagulation

**Abstract** Annexins (Anx) are a family of structurally related proteins that all bind to anionic phospholipids in a  $\text{Ca}^{2+}$ -dependent manner. Some biological properties of beta-2-glycoprotein I ( $\beta_2$ -GPI) are similar to those of Anx IV and Anx V. Urinary trypsin inhibitor (UTI) helps to maintain normal pregnancy and prevent preterm delivery by inhibiting uterine contraction. However, plasma  $\beta_2$ -GPI and UTI levels have not been measured in normal pregnancy. The aim of this study is to clarify the levels of these parameters. Subjects were nonpregnant women ( $n=50$ ), 120 pregnant women, and maternal subjects just after delivery ( $n=53$ ) or postpartum ( $n=67$ ). All of the subjects were healthy. Plasma levels of  $\beta_2$ -GPI, UTI, Anx IV, Anx V and other coagulation and fibrinolysis markers were measured by ELISA. The mean plasma level of  $\beta_2$ -GPI was significantly increased during the third trimester of pregnancy and 3 to 5 days after delivery. The mean plasma level of UTI was unchanged from the first trimester of pregnancy to the postpartum period. The mean plasma UTI level in

*Abbreviations:* Anx, annexins; PL, anionic phospholipids; DIC, disseminated intravascular coagulation;  $\beta_2$ -GPI,  $\beta_2$ -glycoprotein I; UTI, urinary trypsin inhibitor; TF, tissue factor; TAT, thrombin–antithrombin III complex; PIC, plasmin- $\alpha_2$ -plasmin inhibitor complex; IAI, inter- $\alpha$ -trypsin inhibitor; VD, vaginal delivery; CS, cesarean section.

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vaginal delivery group was significantly higher than that in cesarean section group.  $\beta_2$ -GPI protein was expressed in some of the syncytiotrophoblasts. These data suggest that  $\beta_2$ -GPI might act to prevent blood clotting on the placental surfaces and also prevents disseminated intravascular coagulation in the microcirculation and maternal plasma. UTI levels might be kept constant by increased urinary excretion despite overproduction during pregnancy.

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## Introduction

Annexins (Anx) are a family of structurally related proteins that all bind to anionic phospholipids (PL) in a  $\text{Ca}^{2+}$ -dependent manner. Anx IV specifically binds to sialoglycoproteins and glycosaminoglycans [1–5]. Anx V, originally purified from the placenta, plays an important role in preventing activation of the coagulation system, and consequently in keeping slow-moving blood from clotting in the placenta [6]. Correspondence of the amino acid sequence between Anx IV and Anx V is the highest among this family of proteins. Anx IV and Anx V have some of the common biochemical properties, such as binding to carbohydrate or PL [4]. We previously demonstrated that both Anx IV and Anx V show similar anticoagulant activity [7], and that the plasma level of Anx IV suddenly increases after delivery, while Anx V remains low during this period. These results suggested that Anx IV enters the maternal bloodstream just after delivery and might play a role in preventing postpartum disseminated intravascular coagulation (DIC) [7].

Beta-2-glycoprotein I ( $\beta_2$ -GPI) is mainly synthesized in the liver and secreted into the blood [8]. It is mainly found in the lipoprotein-free fraction, but part is associated with lipoproteins [9]. Some biological properties of  $\beta_2$ -GPI are similar to those of Anx IV and Anx V: (i) they are all found in the placenta; (ii) all have affinity for negatively charged phospholipids and heparin glycosaminoglycan; and (iii) they are principal target antigens for antiphospholipid antibodies associated with habitual abortion [9,10]. However, plasma  $\beta_2$ -GPI levels have not been measured in normal pregnancy.

A glycoprotein with a high inhibitory activity against trypsin was isolated in 1961 from human plasma and named inter- $\alpha$ -trypsin inhibitor (ITI), recently inter- $\alpha$  inhibitor (Ial). Since then, several other proteins that share antigenic and structural similarities with Ial have been identified and classified as members of the Ial protein family. Ial is an abundant plasma protein. It consists of three polypeptides: two heavy chains and one light chain

called urinary trypsin inhibitor (UTI) or bikunin [11,12]. Ial molecules are synthesized in hepatocytes, and then secreted into circulation at high concentrations (~0.5 mg/dl). As compared to the amount of Ial, that of UTI in the plasma, which is released from Ial family proteins, is much less. UTI helps to maintain normal pregnancy and prevent preterm delivery by inhibiting uterine contraction [13,14]. Urinary UTI levels are elevated in normal pregnancy [13], but plasma UTI levels during pregnancy have not been investigated.

The aims of the present study were: (1) to determine the plasma  $\beta_2$ -GPI levels and UTI levels in normal pregnancy and postpartum, (2) to reveal the relationships between the levels of plasma  $\beta_2$ -GPI, UTI, Anx IV, Anx V, or other coagulation and fibrinolysis markers, (3) to compare Anx IV, Anx V,  $\beta_2$ -GPI or UTI levels between cesarean section group and vaginal delivery group. The results will be helpful to know the roles and relationships of these molecules during pregnancy and postpartum.

## Materials and methods

### Sample collection of plasma and placenta

The institutional review board approved this study protocol, and all subjects provided informed consent. The subjects were so nonpregnant women, 30 women during the first trimester of pregnancy (10 weeks of gestation), 50 women during the second trimester (24 weeks), 40 women in the third trimester (33 to 34 weeks), 53 mothers just after delivery, and 67 mothers at 3 to 5 days postpartum (Table 1). All of the subjects were healthy and had no complications during pregnancy; none of them developed hypertension, diabetes mellitus, or other diseases. Peripheral blood was collected into tubes containing EDTA or 0.18 M sodium citrate. Plasma was immediately separated by centrifugation at  $1400\times g$  for 15 min at 4 °C, and was stored at –80 °C until analysis.

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