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Research Article

The Ratios of Total Serum Protein to Protein Electrophoretic Fractions during Pregnancy as Diagnostic Information

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Abstract

Background: Ratios of total serum protein (TP) concentrations to serum protein electrophoretic fractions could reflect impact on intravascular homeostasis in pregnancy of qualitative and quantitative changes in high-abundance protein of serum between consecutive trimesters.

Methods: TP concentrations were measured by biuret method and six protein fractions were separated by electrophoresis in 186 serum samples from 65 healthy pregnant women in each trimester of normal singleton pregnancy and from 20 non-pregnant women.

Results: TP/fraction ratios in pregnancy and postpartum period differed from those in non-pregnancy. Ratios of TP/ protein fractions changed across trimesters, mostly between first and second trimesters with increase in TP / albumin ratio by 5% while ratios TP/alpha-1-, TP/alpha-2- and TP/beta-1-globulin decreased by 22%, 15% and 15%, respectively. TP/gamma-globulin ratio increased by 15% between second and third trimesters.

Conclusions: Ratios of TP concentrations to specific protein fractions may reflect trimester-specific qualitative and quantitative changes in serum content of high-abundance proteins and their effect on serum protein homeostasis in pregnancy. Decreased ratios of TP to alpha-1-, alpha-2-, beta-1- and beta-2-globulins confirm increases in concentrations of individual proteins contained in these fractions with development of pregnancy, with largest increase in level of alpha-1-globulin in earliest period of pregnancy.

Keywords: Biomarkers; Electrophoresis; Pregnancy; Serum proteins; Serum protein profile

Abbreviations

NP: Non Pregnant; PP: Postpartum; TP: Total Protein; TP/Protein Fraction Ratio: Total Protein/Protein Fraction Ratio

Background

To date, there are very few specific diagnostic markers that could be used for evaluating complex metabolic processes during pregnancy and predicting their possible effect(s) on postnatal development. Serum protein patterns determined throughout pregnancy seem to offer such valuable biomarkers obtained noninvasively which could aid in differentiating between normal physiological changes and disease pathology in pregnancy.

Each electrophoretically separated serum fraction is characterized by the concentration range for the protein associated with the fraction and the composition of a group of individual proteins with similar electrophoretic mobility, but independently involved in different metabolic processes [1-5]. Protein classification by serum protein electrophoresis is performed for the most abundant twenty-two well-characterized proteins, which account for 99% of the human serum proteome, while the proteins constituting the remaining 1% are difficult to separate electrophoretically and identify due to their very low serum concentrations and a tendency to bind to other proteins [6-8].

Establishing the association between electrophoretic serum protein fractions and serum TP levels in the three trimesters of pregnancy and the postpartum period may help in better understanding of the involvement of individual protein fractions in the maintenance of protein homeostasis during pregnancy [9]. Identification of these protein fractions whose serum concentrations undergo considerable quantitative changes during pregnancy altering their relation to TP may provide preliminary information on their role(s) in specific metabolic processes at various periods of gestation. The ratios of TP to specific electrophoretic protein fractions (TP/protein fraction ratio) might be used throughout gestation as a screening test to identify the qualitative and quantitative changes in the composition of high-abundance proteins in the serum of pregnant women and serve as diagnostic biomarkers of maternal disease and fetal pathology.

The purpose of the study was to assess the TP/protein fraction ratios in the serum of pregnant women, measured trimester by trimester and in the postpartum period (24-48 h after delivery), compared to the concentrations in the sera of non-pregnant controls.

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Material and Methods

Subjects

Prospectively screened 64 healthy women aged 17-43 years (mean ± SD: 31.4 ± 5.8) attending three routine antenatal visits in each trimester of a normal singleton pregnancy: first trimester, pregnancy weeks 8-12 (n=55); second trimester, pregnancy weeks 20-24 (n= 42); third trimester, pregnancy weeks 34-38 (n=39); the postpartum period, 24-48 h after delivery (n=30). The differences in the concentration of the parameters in the serum were statistically assessed between the groups representing subsequent stages of pregnancy. From among 64 examined women, 15 participants were selected, whose blood samples were obtained in each trimester of pregnancy and in the postpartum period (four samples from each woman) and graphically illustrated the dynamics of changes in the examined parameters during pregnancy (Figure 1).

Gestational age was calculated from the first day of the last menstrual period and confirmed by clinical examination. Clinical, laboratory and ultrasound examinations were used to confirm the normal course of pregnancy. The pregnant women were non-smokers and did not receive any anti-inflammatory medication.

The control group consisted of 20 non-pregnant female volunteers aged 21-33 years (mean ± SD: 26.4± 3.1) recruited among hospital staff. All were nonsmokers and had not used hormonal contraception for at least six months prior to blood sample collection. Infections and any other health problems were the exclusion criteria for participation in the study, for both pregnant and non-pregnant subjects.

Blood samples

In total, 186 blood samples were drawn by venipuncture into test tubes, which did not contain an anticoagulant and allowed to clot at room temperature. After centrifugation at 3000g for 10min at 4°C, serum was obtained and aliquots were immediately stored at -80°C until assayed. On the day of the measurements, serum samples were thawed at room temperature using gentle vortexing. This study was approved by the Medical Ethics Committee at the Central Clinical Hospital of the Ministry of the Interior, Warsaw, in accordance with the Declaration of Helsinki, number No 71/2011.

Methods

Serum TP concentrations were measured by the biuret method, using the COBAS c502 analyzer (Roche Diagnostics, Basel, Switzerland) and the dedicated reagents, calibrators and controls, at the Central Clinical Hospital Laboratory in Warsaw.

The serum protein components were separated by electrophoresis into six fractions (albumin, alpha-1 globulins, alpha-2 globulins, beta-1 globulins, beta-2 globulins and gamma-globulins) using the Interlab G26 instrument (Interlab Sebia, Rome, Italy) and commercially available agarose plates for electrophoresis (Interlab Electrophoresis) according to the Manufacturer's instructions. The concentration of total protein is being used to calculate the absolute concentration in g/L of each fraction.

Statistical analysis

Statistical analyses were performed using STATISTICS [StatSoft Inc. (2014) STATISTICA (data analysis software system) version 12. www.statsoft.com]. The results are reported as mean ± SD, median, range, coefficient of variation (CV). Comparisons of serum concentrations of TP and of each protein component between trimesters, after delivery and in controls were made using the Anova rank Tukey-Kramer Multiple Comparisons. The Spearman`s rank order correlation test was performed to express the relationship between protein concentrations. The value of $p<0.05$ was considered to be statistically significant.

Results

The dynamics of changes in serum concentrations of TP and individual protein fractions between trimesters of pregnancy are presented in Figure 2 and 3. Both figures graphically illustrate the individual variability of the concentration of these parameters in 15 participants in all subsequent stages of pregnancy.

Compared to controls (NP: Non-Pregnant), the sera collected

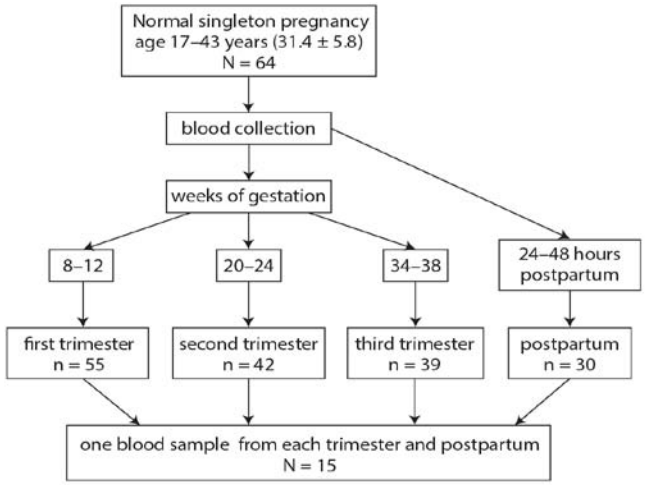

Figure 1: Study group and blood specimen collection schedule.

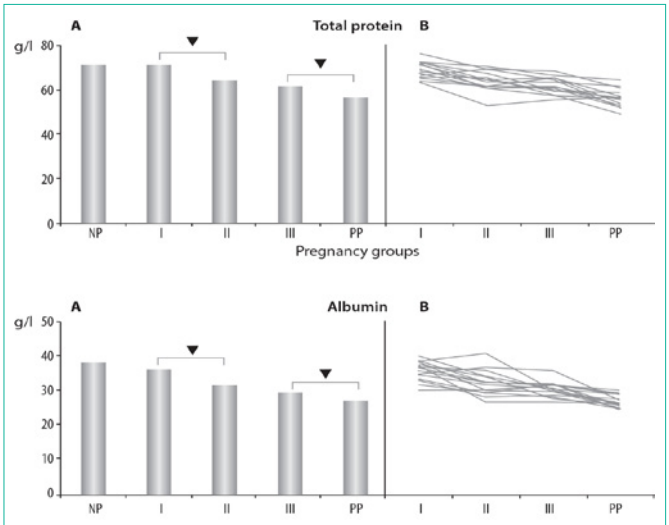

Figure 2: A) Dynamics of changes in the serum concentrations of Total Protein (TP) and albumin in the I (n=55), II (n= 42), III (n=39) trimester of pregnancy and in the Postpartum (PP) (n=30). NP = non-pregnant controls (n=20). ▼Concentration significantly decreased at $p<0.05$. B) Serum concentrations of TP and albumin in a selected individual 15 out of 64 pregnant women in each trimester of pregnancy and in the postpartum (PP).

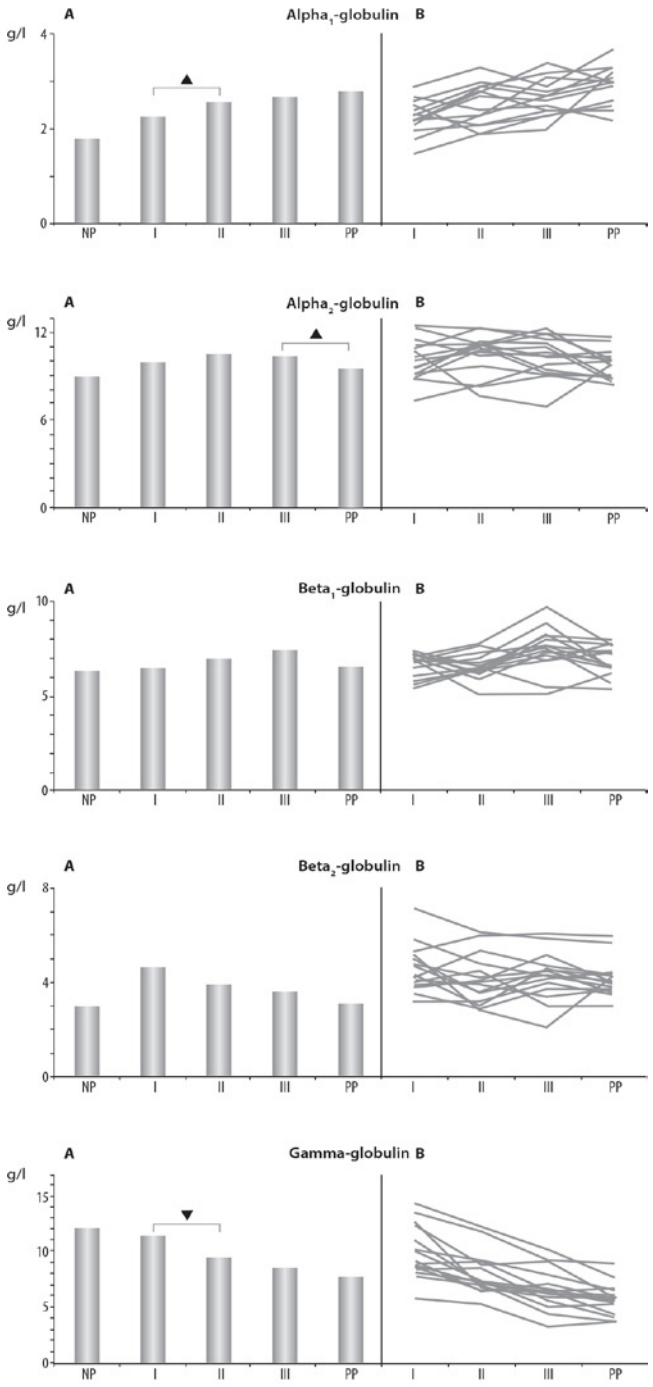

Figure 3: A) Dynamics of changes in the serum concentrations of proteins in the globulin fractions in the I (n=55), II (n= 42), III (n= 39) trimester of pregnancy and in the Postpartum (PP) (n=30). NP: Non-Pregnant controls (n=20). NP: Non-Pregnant controls ▲Alpha-1 globulin concentrations significantly increased at p<0.05. ▼Alpha-2 globulin and gamma-globulin concentrations significantly decreased at p<0.05. B) Serum concentrations of proteins in the globulin fractions in a selected individual 15 out of 64 pregnant women in each trimester of pregnancy and in the postpartum (PP).

in the first, second and third trimesters and after delivery (PP: Postpartum) demonstrated significantly lower concentrations of TP, albumin and gamma globulins and higher concentrations of alpha-1, alpha-2 and beta-1 globulins (p<0.05). A significant fall in

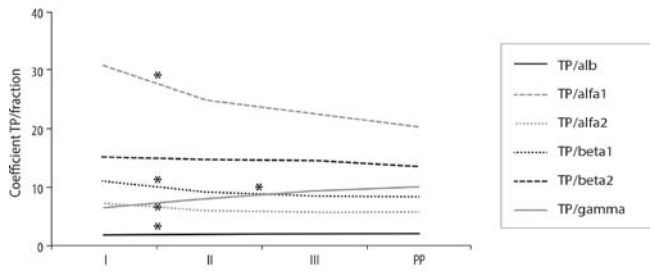

Figure 4: Dynamics of changes in the ratios of serum Total Protein (TP) concentrations to the serum concentrations of proteins in electrophoretic fractions. *Statistically significant changes in each trimester and in the Postpartum (PP) at p<0.05.

the concentrations of TP, albumin and gamma globulins was found between the first and second trimesters with further decreases in the concentrations of TP, albumin and alpha-2 globulin in the third trimester and after delivery. The only increase in concentration was observed for alpha-1-globulin, from the first to the second trimester.

Table 1 presents the differences in the ratios of TP to individual protein fractions (TP/fractions) changing throughout pregnancy, compared with the control non-pregnant group.

In the first trimester, the TP/fraction ratios for alpha-1-, alpha-2- and beta-2 globulins were significantly lower while there were no differences in the ratios of TP to albumin, beta-1 and gamma globulin between pregnant women and controls. In the second and third trimesters and after delivery the TP/albumin and TP/gamma-globulin ratios were higher and the TP/alpha-1-, TP/alpha-2- , TP/beta-1- and TP/beta-2-globulin ratios were lower compared with the control sera (Figure 4).

The dynamic changes (p<0.05) in the TP/fraction ratios during pregnancy shown in Figure 4 were observed mostly between the first and second trimesters, with only a slight increase in the TP/albumin ratio (by ca. 5%) and a decrease in the ratios of TP/alpha-1-, TP/alpha-2 and TP/beta-1- globulins, by 22%, 15% and 15%, respectively, with no further changes in these ratios between the second and third trimesters and the postpartum period. Changes in the TP/gamma-globulin ratio were subject-specific, with an increase from the second to the third trimester (by ca. 15% on average) and without any significant changes in the postpartum period.

The correlations between the serum concentrations of TP and individual protein fractions during the three trimesters of pregnancy and in the postpartum period are presented in Table 2.

These correlations demonstrated characteristic differences between the trimesters and the postpartum period. Albumin was the only electrophoretic protein fraction, which maintained stable correlations with varying TP concentrations throughout pregnancy and in the postpartum period. With the continuation of pregnancy, albumin and gamma globulins demonstrated weak correlations with other protein fractions. Strong, statistically significant correlations between the concentrations of alpha-1-, alpha-2-, beta-1- and beta-2-globulins were observed throughout pregnancy and in the postpartum period.

Table 1: Changes in the ratios of individual protein concentrations in electrophoretic fractions to the Total Protein (TP) concentrations in maternal sera in each trimester of pregnancy and in the postpartum, and the TP/fraction ratios in non-pregnant controls.

Total protein/fraction ratio	Mean ± SD *(CV)* ***median*** **(***range***)**					***ANOVA***
	Trimesters of pregnancy			**Post Partum**	**Controls**	***P***
	I (n=55)	**II (n=42)**	**III (n=39)**	**(n=30)**	**(n=20)**	
TP/albumin	1.96 ± 0.16 *(8.16)* *1.93* (1.59-2.40)	2.06 ± 0.13 *(6.31)*▲ *2.07* (1.69-2.32)	2.09 ± 0.14 *(6.70)* ▲ *2.12* (1.38-2.30)	2.07 ± 0.20 *(8.02)* ▲ *2.09* (1.15-2.31)	1.87 ± 0.15 *(8.02)* *1.90* (1.65-2.17)	<0.0001
TP/alpha-1-globulins	31.76 ± 6.76 *(21.28)* ▼ *30.91* (20.57-50.67)	24.92 ±3.64 *(14.61)*▼ *24.45* (19.09-39.38)	22.96 ± 2.30 *(10.02)*▼ *22.59* (19.12-28.50)	20.10 ± 3.15 *(15.67)* ▼ *19.64* (14.17-25.79)	39.97 ± 5.30 *(13.26)* *39.71* (31.67-53.89)	<0.0001
TP/alpha-2-globulins	7. 18 ± 1.09 *(15.18)* ▼ *7.26* (5.24-10.27)	6.15 ± 0.66 *(10.73)* ▼ *6.12* (5.08-7.98)	5.98 ± 0.64 *(10.70)* ▼ *5.93* (4.92-8.14)	5.88 ± 0.49 *(8.33)* ▼ *5.93* (5.00 - 6.75)	8.08 ± 1.35 *(16.71)* *7.86* (6.63-13.21)	<0.0001
TP/beta-1-globulins	10.95 ± 1.80 *(16.44)* *10.91* (6.54-15.00)	9.31 ± 1.18 *(12.67)* ▼ *9.33* (7.36-11.77)	8.51 ± 1.32 *(15.51)* ▼ *8.31* (6.19-14.00)	8.45 ± 0.94 *(11.12)*▼ *8.42* (6.62-10.18)	11.46 ± 1.99 *(17.36)* *11.65* (5.88-14.62)	0.0001
TP/beta-2-globulins	15.13 ± 2.82 *(18.64)* ▼ *14.80* (9.86-23.44)	14.73 ± 3.06 *(20.77)*▼ *14.55* (9.24-23.00)	14.43 ± 2.78 *(19.27)* ▼ *14.05* (10.68-27.14)	13.52 ± 1.79 *(13.24)*▼ *13.25* (10.67-18.33)	18.59 ± 5.70 *(30.66)* *18.05* (10.91-31.74)	<0.0001
TP/gamma-globulins	6.93 ± 1.58 *(22.80)* *6.67* (3.60-11.70)	8.15 ± 1.57 *(19.26)* ▲ *8.16* (5.57-13.11)	9.50 ± 2.61 *(27.47)* ▲ *9.22* (5.73-17.50)	10.00 ± 2.76 *(27.60)*▲ *9.15* (6.83-20.77)	6.50 ± 1.48 *(22.77)* *6.48* (4.53-10.44)	<0.0001

▲Significantly increased compared with controls; ▼Significantly decreased compared with controls.

Discussion

The results show significant differences in the TP/protein fraction ratios measured in the serum during pregnancy and in non-pregnant female controls, and between the trimesters of pregnancy and the postpartum period. Lower ratios of TP to alpha-1-, alpha-2- and beta-2- globulins throughout pregnancy and in the postpartum period, and to albumin and gamma globulins starting from the second trimester demonstrate dramatic qualitative and quantitative physiological variations in the serum concentrations of the proteins contained in these fractions and their consistent occurrence at particular periods of gestation.

The obtained results raise unexplained questions about the mechanisms regulating intravascular protein homeostasis and the possibility of practical use of the mutual proportions between TP and subfraction ratios in differentiating dynamic physiological changes seen during pregnancy and pathological changes. Calculation of the TP/protein fraction ratio eliminates the effect of expanding plasma volume characteristic of pregnancy and allows comparing protein concentrations between trimesters and between individual women [10]. The TP/protein fraction ratio might be used to establish the reference intervals for individual serum proteins as diagnostic biomarkers in pregnancy. It remains to be decided whether establishing the reference intervals for the TP/protein fraction ratios in the serum of pregnant women might prompt its use in clinical practice as a screening test for abnormalities of pregnancy, to be followed, when values outside the reference range are measured, by further measurements of specific proteins.

Another theoretical possibility to use of these ratios may be to provide information of their diagnostic role in specific metabolic processes. Comparison of the TP/protein fraction ratios between trimesters and after delivery might aid in understanding of changing biological roles of individual proteins at various periods of pregnancy. The characteristic correlations between these serum fractions may result from their coincident involvement in the regulation of the same biological process(es) important for the developing fetus and point to members of the globulin fraction as putative biomarkers to follow the course of pregnancy. Documented changes in the TP/protein fraction ratio for individual electrophoretic fractions observed across trimesters confirm the differences in the quantitative and qualitative composition of serum total protein during pregnancy and may lead to further testing of specific proteins as screening.

Importantly for obstetric practice, it should be elucidated which individual serum proteins involved in specific processes of prenatal development could be used as diagnostic markers at various periods of gestation. The total protein represents the sum of thousands of proteins/peptides in the human blood serum at concentrations ranging from 35 to 50 x 10^9pg/mL. The serum TP concentration reflects the equilibrium between synthesis and depletion of individual proteins in the human body. Based on the results of this study, the calculated TP/protein fraction ratios for high-abundance serum proteins might offer new biomarkers to identify and assess changes in the maternal-fetal-placental unit in each trimester of pregnancy [5,6,11,12]. The largest decrease observed for the TP/alpha-1-globulin ratio seems to suggest a strong association between the components of this fraction and changes in the concentrations of acute-phase proteins (alpha-1-antitrypsin, orosomucoid) and numerous transport proteins of vital importance for fetal development (vitamin-D-binding proteins, thyroid-binding protein, transcortin, alpha-fetoprotein) occurring as soon as the earliest stage of pregnancy [1,11,13,14]. The decrease in the TP/alpha-2-globulin ratio may be attributable to changes in the concentrations of alpha-2-macroglobulin and haptoglobin while transferrin may be responsible for the fall in the TP/beta-1-globulin ratio. A slight increase in the TP/albumin ratio (by ca. 5%) which exhibited much slower dynamics of changes than the ratios of TP to all globulin fractions is due to a decrease in the concentration of albumin, the most abundant electrophoretic protein fraction . Weak evidence is whether serum albumin is a marker of malnutrition in non-inflammatory states such as starvation [15]. It remains unclear whether slight decreases in the albumin levels observed in this study could gradually deplete serum albumin reserve for binding of bilirubin, a wide variety of drugs, bile acids, copper, zinc, calcium and magnesium, vitamin D and thyroxin, reduce colloidal osmotic pressure and antioxidant activity [4,16,17]. Increases in the TP/gamma-globulin ratio between the second and third trimesters of pregnancy confirm the hypothesis put forward by other authors of transplacental transfer of gamma globulins from the maternal circulation to the fetus. Maternal transfer IgG antibodies to the fetus as the only antibodies class provides essential for protection to the infant while his / her humoral response is inefficient. IgG transfer depends on the maternal levels of total IgG, gestational age, placental integrity [18,19].

Table 2: Correlation coefficients between the serum concentrations of Total Protein (TP) and electrophoretic fractions and the correlations among fractions in each trimester of pregnancy (I, II, III) and in the Postpartum (PP). Significant correlations ($p<0.05$) are marked in bold.

Electrophoretic fraction	*vs*	I	II	III	PP
Total Protein	Albumin	0.525	0.637	0.596	0.843
	$Alfa_1$	-0.202	0.351	0.679	0.244
	$Alfa_2$	-0.136	0.378	0.594	0.704
	$Beta_1$	0.027	0.394	0.522	0.444
	$Beta_2$	0.073	0.23	0.611	0.771
	Gamma	0.040	0.599	0.722	0.643
Albumin	$Alfa_1$	-0.172	-0.18	-0.174	-0.119
	$Alfa_2$	-0.379	-0.111	-0.055	0.067
	$Beta_1$	-0.241	-0.09	0.06	-0.116
	$Beta_2$	-152	-0.252	0.263	0.285
	Gamma	0.213	0.131	-0.02	0.497
Alpha-1	Albumin	-0.172	-0.18	-0.174	-0.119
	$Alfa_2$	0.737	0.513	0.584	0.409
	$Beta_1$	0.521	0.354	0.482	0.328
	$Beta_2$	0.391	0.466	0.353	0.254
	Gamma	0.077	0.175	0.312	-0.169
Alpha-2	Albumin	-0.379	-0.111	-0.055	0.067
	$Alfa_1$	0.737	0.513	0.584	0.409
	$Beta_1$	0.545	0.350	0.486	0.583
	$Beta_2$	0.41	0.496	0.529	0.514
	Gamma	-0.172	-0.013	0.146	0.179
Beta-1	Albumin	-0.241	-0.090	0.060	-0.116
	$Alfa_1$	0.521	0.354	0.482	0.328
	$Alfa_2$	0.545	0.350	0.486	0.578
	$Beta_2$	0.334	0.233	0.419	0.440
	Gamma	0.058	0.106	0.090	0.133
Beta-2	Albumin	-0.152	-0.252	0.263	0.285
	$Alfa_1$	0.391	0.466	0.353	0.254
	$Alfa_2$	0.481	0.496	0.529	0.514
	$Beta_1$	0.334	0.233	0.419	0.440
	Gamma	-0.034	-0.03	0.299	0.611
Gamma	Albumin	0.213	0.131	-0.02	0.497
	$Alfa_1$	0.077	0.175	0.312	-0.169
	$Alfa_2$	-0.172	-0.013	0.146	0.179
	$Beta_1$	0.058	0.106	0.090	0.133
	$Beta_2$	-0.034	-0.03	0.299	0.611

Serum total protein and its fractions in pregnancy.

The results here reported show that the most dynamic changes in the TP/protein fraction ratio occurred between the first and second trimesters, but the rate at which the value decreased varied from 22% for alpha-1-globulin to 15% for alpha-2-globulin and beta-1-globulin. The question arises whether the obtained results can facilitate the understanding of their diagnostic significance and confirm their utility in clinical practice? Dynamic decreases in the ratios of TP to alpha-1, alpha-2 and beta-2-globulin seen between the first and second trimesters are especially interesting as that proves the exceptional role(s) individual proteins in these fractions have in the metabolic processes of early pregnancy. The diagnostic significance of this finding is supported by the observation by Olooto [20] that the early stage of placental abnormality during the first trimester with consequent placental insufficiency and release of placental materials into the maternal circulation is asymptomatic. Also, the question of the effect of inflammation on the outcome of pregnancy and maternal health in early pregnancy and its later stages has not been yet satisfactorily answered [21,22].

Conclusions

Significant changes in TP/protein fraction ratio might be a useful screening test to detect qualitative and quantitative changes in the composition of high-abundance proteins in the serum with the continuation of pregnancy. The most dynamic changes in the TP/protein fraction ratio early in pregnancy reflect complex metabolic processes with the involvement of serum abundant proteins and indicates the need to understand their role in maintaining intravascular homeostasis during this period.

Declarations

Ethical approval: This study was approved by the Medical Ethics Committee at the Central Clinical Hospital of the Ministry of the Interior, Warsaw, in accordance with the Declaration of Helsinki, number No 71/2011.

Consent to participate: Written consent for participation in the study was obtained from each pregnant and non-pregnant subject.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

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Author contributions: Lisowska-Myjak B. (BLM): Conception, analyzed the data, final approval of the version to be published; Skarżyńska E. (ES): Drafting the article; Zborowska H. (HZ): Design of the study; Strawa A. (AS): Acquisition of data; Jakimuk A. (AJ): Analysis and interpretation data.

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