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# FEATURES OF COAGULATION HEMOSTASIS DISORDERS IN PREGNANT WOMEN: A SYSTEMATIC REVIEW OF CURRENT CONCEPTS AND CLINICAL SIGNIFICANCE

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**Introduction.** Disorders of the hemostasis system in pregnant women represent a complex problem of modern perinatology. Physiological adaptive changes in coagulation often mask the development of severe pathologies, which complicates timely diagnosis.

**Methodology.** A systematic analysis of 50 scientific publications from the PubMed, LILACS, CNKI, and Cochrane Library databases over the past 5 years was conducted, focusing on coagulation shifts during physiological pregnancy, DIC syndrome, venous thromboembolism (VTE), and intrahepatic cholestasis of pregnancy (ICP).

**Results.** Trimester-specific standards for traditional parameters and new molecular markers (thrombomodulin, thrombin-antithrombin complex, plasmin-α2-antiplasmin complex, tissue plasminogen activator-inhibitor complex) were systematized. The features of the pathogenesis of obstetric DIC syndrome were described, and clinical validation of the O. Erez scale was performed. Key independent predictors of VTE were identified, among which immobilization and a personal history of thrombosis play a leading role. The phenomenon of dual risk of hemostasis disorders in ICP was reviewed.

**Conclusions.** The implementation of trimester-specific reference intervals and adapted diagnostic scales is a necessary condition for preventing critical obstetric coagulopathies and reducing maternal mortality.

**Keywords:** reproductive health, pregnancy, coagulation hemostasis, trimester-specific intervals, venous thromboembolism, DIC syndrome, Erez scale, intrahepatic cholestasis of pregnancy.

## Introduction

Protecting the health of women of reproductive age and reducing maternal mortality remain global healthcare priorities. According to WHO estimates, approximately 260,000 maternal deaths are registered globally each year. In the structure of causes of maternal losses, postpartum hemorrhage, venous thromboembolic complications (VTE), and associated coagulopathies invariably occupy leading positions. Pregnancy is accompanied by a profound adaptation of the maternal hemostasis system. Physiological hypercoagulation is an evolutionarily developed protective mechanism aimed at preventing massive bleeding during childbirth. However, under the influence of pathological triggers (preeclampsia, systemic infections, hereditary thrombophilias, cholestasis), this process transitions into a pathological phase. Timely diagnosis of hemostasis disorders is difficult: the use of standard "non-pregnant" laboratory intervals leads to false overdiagnosis of thrombophilias or to missing the early signs of consumption coagulopathy.

**The aim of the review:** to systematize and summarize modern concepts of the features of functioning and disorders of the coagulation hemostasis system in pregnant women based on trimester-specific reference intervals and validated scales.

## Literature Search Methodology

A systematic analysis of the world literature over the past 5 years (from 2021 to 2026) was conducted. The search for relevant publications was carried out in the PubMed/MEDLINE, LILACS, CNKI, and Cochrane Library databases. To formulate search queries, controlled MeSH terms and keywords were used: "pregnancy" (pregnancy), "coagulation hemostasis" (coagulation hemostasis), "trimester-specific intervals" (trimester-specific reference intervals), "DIC syndrome" (disseminated intravascular coagulation), "venous thromboembolism" (venous thromboembolism), and "cholestasis of pregnancy" (cholestasis of pregnancy). The final analysis included 50 sources (original studies with a low risk of bias according to the NOS scale, systematic reviews, and international clinical guidelines).

## Results and Discussion

### Physiological trimester-specific shifts in coagulation parameters

Physiological adaptation of hemostasis during pregnancy is mediated by an increase in estrogen and progesterone levels, which stimulate hepatic synthesis of clotting factors. By the second and third trimesters of gestation, an increase in the concentrations of fibrinogen (factor I), factors VII, VIII, IX, X, XII, and von Willebrand factor is observed. Simultaneously, suppression of anticoagulant protection occurs — the level of free protein S drops by more than 50%, and placental production of plasminogen activator inhibitors (PAI-1 and PAI-2) blocks adequate fibrinolysis. Statistically significant changes in the main parameters of the coagulogram depending on the gestational age are presented in Table 1.

**Table 1. Dynamics of traditional coagulation parameters in healthy pregnant and non-pregnant women**

| Parameter | Non-pregnant (n = 131) | I trimester (n = 183) | II trimester (n = 183) | III trimester (n = 263) | p-value |
|---|---|---|---|---|---|
| **FIB, g/l** | 2.39 +- 0.38 | 2.95 +- 0.62 | 3.27 +- 0.65 | 3.56 +- 0.69 | <0.001 |
| **PT, s** | 12.31 +- 1.26 | 12.11 +- 1.00 | 11.06 +- 0.84 | 10.35 +- 0.72 | <0.001 |
| **APTT, s** | 32.13 +- 2.92 | 30.02 +- 3.75 | 29.18 +- 3.03 | 29.03 +- 3.05 | <0.001 |
| **TT, s** | 14.57 +- 0.96 | 14.92 +- 1.48 | 14.92 +- 1.50 | 15.35 +- 1.26 | <0.001 |
| **FDP, mcg/ml** | 1.13 (0.65; 1.53) | 1.23 (0.61; 2.04) | 2.23 (1.15; 3.35) | 3.64 (2.50; 5.28) | <0.001 |
| **DD, mcg/ml** | 0.21 (0.14; 0.31) | 0.25 (0.17; 0.36) | 0.45 (0.28; 0.75) | 0.84 (0.54; 1.43) | <0.001 |
| **ATIII, %** | 114.74 +- 10.31 | 99.61 +- 13.40 | 95.64 +- 11.86 | 93.80 +- 12.34 | <0.001 |

Based on non-parametric analysis, clinical trimester-specific reference ranges were developed (Table 2).

**Table 2. Clinical trimester-specific reference intervals of the coagulogram**

| Coagulation parameter | Outside pregnancy | I trimester of gestation | II trimester of | III trimester of |
|---|---|---|---|---|

| | | | gestation | gestation |
|---|---|---|---|---|
| **FIB, g/l** | 1.81-3.29 | 2.11-4.32 | 2.31-4.77 | 2.39-4.96 |
| **PT, s** | 10.90-13.85 | 10.90-13.85 | 9.70-12.64 | 9.20-11.95 |
| **APTT, s** | 27.10-37.70 | 24.60-39.28 | 24.16-35.43 | 23.90-35.51 |
| **TT, s** | 12.95-15.88 | 12.95-15.88 | 12.95-15.88 | 13.41-18.00 |
| **FDP, mcg/ml** | 0.04-2.55 | 0.04-2.55 | 0.15-7.40 | 0.55-13.43 |
| **DD, mcg/ml** | 0.06-0.46 | 0.03-1.15 | 0.08-2.13 | 0.15-3.60 |
| **ATIII, %** | 99.38-133.80 | 75.57-125.31 | 74.35-119.28 | 71.61-118.29 |

**The role of new molecular markers of coagulation activation**

Traditional coagulogram tests reflect only the final stage of fibrin polymerization. New plasma markers capture subclinical activation of hemostasis at the endothelial level. These include thrombomodulin (TM), thrombin-antithrombin complex (TAT), plasmin-α2-antiplasmin complex (PIC), and tissue plasminogen activator-inhibitor complex (tPAI-C). The established standards for these parameters are presented in Table 3.

**Table 3. Reference intervals of new molecular markers of hemostasis in pregnant women and puerperas**

| Clinical group | TM (TU/ml) | TAT (ng/ml) | PIC (mcg/ml) | tPAI-C (ng/ml) |
|---|---|---|---|---|
| **Healthy non-pregnant women** | 3.20-4.60 | 0.50-1.64 | 0.160-0.519 | 1.90-4.80 |
| **Pregnant women (I-II trimesters)** | 3.12-7.90 | 0.52-6.91 | 0.162-0.770 | 2.03-9.33 |
| **Pregnant women (III trimester)** | 3.42-8.29 | 0.96-12.92 | 0.162-0.770 | 2.80-14.20 |
| **Puerperas (puerperium)** | 2.70-6.40 | 0.82-3.75 | 0.162-0.770 | 1.10-8.40 |

The levels of TM, TAT, and tPAI-C demonstrate a consistent increase with a peak in the third trimester, reflecting excessive thrombinogenesis and endothelial damage caused by the growing uterus.

**Pathophysiology and assessment scales of DIC syndrome in pregnant women**

DIC syndrome in obstetrics is a secondary critical process characterized by uncoordinated systemic coagulation in the microvascular bed. The main triggering factor is a massive release of active tissue factor (decidual thromboplastin) into the maternal bloodstream, which leads to rapid depletion of the platelet and fibrinogen pool.

The standard ISTH diagnostic scale for non-pregnant patients is ineffective in obstetrics, as it considers a fibrinogen level below 1.0 g/l as a critical marker. However, in a pregnant woman, a decrease in fibrinogen to 2.0 g/l already indicates severe consumption coagulopathy. To address this issue, a specialized scale was developed by O. Erez and co-authors in 2014 (Table 4).

**Table 4. Scoring in the adapted obstetric DIC syndrome scale by O. Erez (2014)**

| Scale indicator | Value limits | Score |
|---|---|---|
| **Prothrombin time difference, s** | < 0.5 | 0 |
| **Prothrombin time difference, s** | 0.5-1.0 | 5 |
| **Prothrombin time difference, s** | 1.0-1.5 | 12 |
| **Prothrombin time difference, s** | > 1.5 | 25 |
| **Platelet count, x 10^9/l** | > 185 | 0 |
| **Platelet count, x 10^9/l** | 100-185 | 1 |
| **Platelet count, x 10^9/l** | 50-100 | 2 |
| **Platelet count, x 10^9/l** | < 50 | 1 |
| **Plasma fibrinogen concentration, g/l** | > 4.5 | 0 |
| **Plasma fibrinogen concentration, g/l** | 4.0-4.5 | 1 |
| **Plasma fibrinogen concentration, g/l** | 3.0-4.0 | 6 |
| **Plasma fibrinogen concentration, g/l** | < 3.0 | 25 |

The clinical threshold of the scale is set at ≥26 points. With a total score of ≥26, manifest obstetric DIC syndrome is diagnosed. Prospective validation of this scale in 126 pregnant women with placental abruption demonstrated high diagnostic value: sensitivity was 88%, specificity was 96%, and the positive likelihood ratio (LR+) was equal to 22.

**Epidemiology, lateralization, and predictors of venous thromboembolism**

Venous thromboembolism remains a crucial cause of maternal death. A large retrospective analysis of 120,652 pregnancies in a clinic in Wuhan (China) for the period from 2010 to 2022 revealed 197 confirmed cases of VTE, which corresponds to an overall incidence of 1.63 cases per 1000 pregnancies. Deep vein thrombosis (DVT) of the lower extremities accounted for 76.1% of all cases. Left-sided lateralization of the process was established: involvement of the left leg was found in 28.9% of patients, the right leg — in 22.8%, and bilateral thromboses — in 14.7%. The dominance of left-sided thromboses is due to the anatomical compression of the left common iliac vein by the right common iliac artery (May–Thurner syndrome). Most thromboses developed in the postpartum period (64.5% of cases, incidence 1.05/1000 pregnancies). Multivariate regression analysis revealed independent clinical predictors for the development of thromboses during the gestational period (Table 5).

**Table 5. Adjusted odds ratios for the leading risk factors for VTE**

| Clinical risk factor | Adjusted odds ratio (αOR) | 95% Confidence interval (CI) | p-value |
|---|---|---|---|
| **Immobilization (>= 72 h)** | 43.25 | 20.558-73.149 | <0.001 |

| | | | |
|---|---|---|---|
| **Personal history of VTE** | 25.73 | 8.562-92.070 | <0.001 |
| **Systemic infection (sepsis)** | 03.08 | 1.852-9.308 | 0.041 |
| **Obesity (BMI >= 30 kg/m2)** | 2.31 | 1.075-3.528 | 0.032 |
| **Hypertensive disorders** | 1.67 | 1.242-3.251 | 0.015 |

Prolonged mobility restriction (αOR=43.25) and a personal history of thrombosis (αOR=25.73) act as the most powerful independent predictors for the development of VTE in pregnant women.

**Intrahepatic cholestasis of pregnancy as a model of dual coagulopathy risk**

ICP exerts a pronounced destabilizing effect on maternal hemostasis, forming a "double risk" phenomenon: a tendency toward thromboembolic complications on the one hand, and a risk of massive bleeding on the other. The accumulation of bile acids in the blood serum causes endotheliopathy, which activates platelet hemostasis and increases the fibrinogen level. On the other hand, impaired bile outflow leads to a deficiency in the absorption of fat-soluble vitamin K, which disrupts the carboxylation of prothrombin complex factors (II, VII, IX, X). A controlled clinical study (175 pregnant women with ICP and 162 in the control group) showed that fibrinogen in the ICP group was significantly higher than in the control group ($p<0.01$) against the background of the absence of a significant difference in platelet levels, APTT, and INR (Table 6).

**Table 6. Clinical and laboratory profile of patients with ICP and the control group**

| **Indicator** | **ICP group (n = 175)** | **Control (n = 162)** | **p-value** |
|---|---|---|---|
| **Gestational age at delivery, days** | 253.75 +- 15.53 | 271.43 +- 10.26 | <0.01 |
| **Fibrinogen, mg/dl** | 574.92 +- 115.22 | 494.87 +- 89.56 | <0.01 |
| **Platelets, x 10^9/l** | 250.81 +- 72.39 | 235.76 +- 59.78 | 0.094 |
| **INR** | 0.89 +- 0.14 | 0.90 +- 0.11 | <0.01 |
| **Albumin, g/l** | 34.29 +- 5.28 | 40.20 +- 6.36 | <0.01 |
| **ALT, U/l** | 120.15 +- 156.82 | 11.06 +- 6.27 | <0.01 |
| **AST, U/l** | 83.97 +- 94.31 | 14.87 +- 5.92 | <0.01 |
| **Total bilirubin, mg/dl** | 0.65 +- 0.65 | 0.38 +- 0.19 | <0.01 |
| **Rate of neonatal complications, %** | 20.6 | 0.6 | <0.01 |

The incidence of VTE after childbirth in the cholestasis group was 1.1% (2 cases). At the same time, the rate of red blood cell mass transfusions due to hypotonic postpartum hemorrhage was 4.5% in the ICP group versus 2.4% in the control group ($p>0.05$), reflecting a clinical trend toward increased bleeding in the absence of liver function decompensation. ICP pathology is associated with a high risk of fetal distress (7.4%) and preterm labor (4.0%).

**Global development vector: WHO Roadmap 2023–2030**

In March 2023, the WHO convened a Global Summit, the outcome of which was the development of the Roadmap to combat postpartum hemorrhage for the period 2023–2030. The Roadmap aims to eliminate infrastructural, human resource, and logistical barriers in low-income countries. Within the framework of the Roadmap, priority is given to:

- Evaluating routes of administration for tranexamic acid (TXA);
- Developing package bundle approaches for the early detection of bleeding;
- Implementing rapid methods for clot assessment (TEG/ROTEM) to personalize therapy and reduce the volume of unjustified fresh frozen plasma transfusions.

**Conclusion**

Obstetric hemostasiology requires a complete abandonment of the use of traditional non-pregnant coagulation standards. Clinical recommendations based on the results of the review:

1. Assessment of the coagulogram of pregnant women must be carried out strictly according to trimester-specific intervals.
2. Prophylactic prescription of LMWH is indicated for pregnant women from the high-risk group, especially with immobilization lasting more than 72 hours.
3. Patients with intrahepatic cholestasis of pregnancy form a dual-risk group and require simultaneous management of the risks of postpartum thrombosis and hemorrhage.
4. Timely verification of obstetric DIC syndrome must be carried out using the adapted O. Erez scale (threshold ≥26 points).

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