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SERUM LEVELS OF COAGULATION-FIBRINOLYSIS FACTORS IN NORMAL PREGNANCY, LABOR AND PUERPERIUM AND IN CESAREAN SECTION DELIVERY

BY

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ABSTRACT

Plasma levels of fibrinopeptide A (FPA), fibrinopeptide Bβ15–42 (FPBβ15–42), high molecular weight kininogen (HMW-kg), kinin, prekallikrein and kallikrein inhibitor during pregnancy, labor, cesarean section and puerperium were studied in 170 cases of full term normal delivery and 20 cases of cesarean section delivery with 30 non-pregnant women taken as control. Significant increases of FPA, FPBβ 15–42 and kinin during normal delivery and puerperium were found. There was also a significant increase of FPA in the uterine venous blood during cesarean section. Significant decrease of HMW-kg during normal labor and also significant decrease of prekallikrein and kallikrein inhibitor after cesarean section were also seen. Our findings suggested that the hypercoagulable state during pregnancy is due to the increase of thrombin and plasmin activity, and the kallikrein-kinin system may be related to the onset of labor and post-delivery uterine contraction. Increase of the FPA in the uterine blood promoted localised coagulation activity during cesarean section.

Key words: Coagulation-fibrinolysis, Pregnancy, Labor, Delivery, Puerperium, Cesarean section.

INTRODUCTION

Many researchers have reported[1–6] that a state of hypercoagulability appeared during pregnancy, Mutoh *et al.*[7] also confirmed that hypercoagulability with hypofibrinolysis existed during normal pregnancy and labor. The purpose of this present work was to study the activities of thrombin and plasmin in the coagulation-fibrinolysis system and to find out the relationship between the kallikrein-kinin system and onset of labor in normal pregnancy and delivery and in cesarean-section delivery.

MATERIALS AND METHODS

One hundred and seventy cases of normal gravidas from the early stage to term pregnancy (from 4 to 42 weeks of gestation) and 20 cases of full term delivery by cesarean section before the onset of labor were chosen as subjects for this study from January 1982 to December 1984. All blood samples for the measurement of fibrinopeptide A (FPA), fibrinopeptide Bβ15–42 (FPBβ15–42), high molecular weight kininogen (HMW-kg) and kinin were taken sequentially according to a prefixed time schedule at the first, second

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Table 1. Plasma levels of fibrinopeptide A, fibrinopeptide Bβ15–42, HMW-kininogen and kinin during normal pregnancy, labor and puerperium

	Not pregnant (n=30)	During Pregnancy				Full term normal delivery, puerperium				
		n	1st trimester	2nd trimester	3rd trimester	n	1st stage labor	2nd stage labor	15 min after delivery	3hrs. after delivery
FPA (ng/ml)	1.0± 0.5	170	1.1± 0.5	2.1± 0.9 *	2.7± 1.2 *	18	3.2± 1.4	5.0± 1.7 #	30.9±22.8 #	9.8± 5.6 #
FPBβ15–42 (ng/ml)	3.3± 1.8	170	4.1± 2.1	6.3± 3.4 *	9.7± 4.6 *	18	10.2± 4.0	13.8± 5.4 #	20.5± 6.9 #	23.4± 9.6 #
HMW-kg (%)	82.6±26.6	140	97.2±29.5	101.1±21.0 *	94.6±23.4	14	62.7±20.5 #	80.5±31.6 #	74.2±31.9	65.1±26.4
Kinin (pg/ml)	10.8± 3.4	170	11.4± 3.8	12.4± 3.5	12.1± 3.8	30	17.1± 7.7 #	16.7± 7.6 #	14.7± 7.1 #	18.9±11.1

Mean±SD *P<0.05 compared to non-pregnancy
#P<0.05 compared to 3rd trimester

and third trimesters, first and second stages of labor and 15 minutes and 3 hours after normal delivery. In the cesarean-section delivery cases, assays were performed on the samples collected before and during the operation and at 3, 6, 12 and 48 hours postoperatively. Simultaneous collections of peripheral and uterine venous blood at 20 to 30 minutes after delivery of the placenta during the operaton were also taken for assay. Determinations of prekallikrein and kallikrein inhibitor in the cesarean cases were also performed. The FPA and FPBβ15–42 were measured according to the methods described by Nossel[8] and Kudryk[9] and the polyethylene glycol method[10] by using the radioimmunoassay kits developed by IMCO. Co., Ltd., Stockholm, Sweden. HMW-kg was measured by the active partial thromboplastin time (APTT) using Fitzgerald factor's deficient plasma. Plasma kinin determination was done by radioimmunoassay[11] and the prekallikrein and kallikrein inhibitors were determined by using substrate S-2302[12] and according to the procedures instructed by Kabi Diagnostica, Stockholm, Sweden. The results were expressed as mean±standard deviation (M±SD) and the data were analysed statistically with Student's t test for the comparision of the mean values ($P<0.05$).

Results

The mean±SD levels of FPA and FPBβ15–42 in normal non-pregnant women were 1.0±0.5 ng/ml and 3.3±1.8 ng/ml, respectively, and in the pregnant women, as pregnancy progressed, the levels of both FPA and FPBβ15–42 increased gradually from mid-term pregnancy (FPA=2.1±0.9, FPBβ15–42 =6.3±3.4, $P<0.05$) and increased markedly during the third trimester of pregnancy. During the second stage of labor in normal delivery, these fibrinopeptides increased significancy ($P<0.05$). In puerperium, the level of FPA continued increasing significantly and reached the peak of 30.9±22.8 at 15 minutes after delivery; FPBβ15–42 also increased significantly and reached the peak of 23.4±9.6 at 3

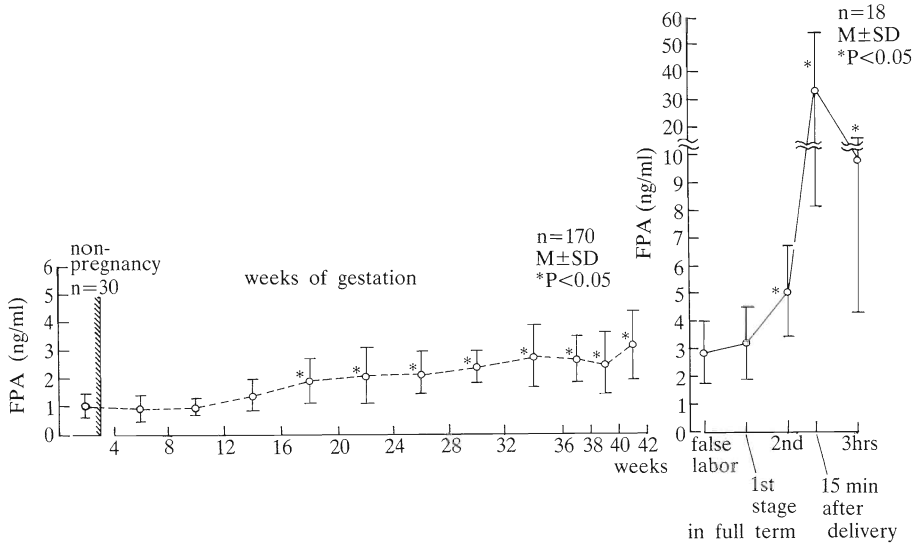

Fig. 1. Fluctuations of fibrinopeptide A (FPA) ng/ml during pregnancy, labor and puerperium

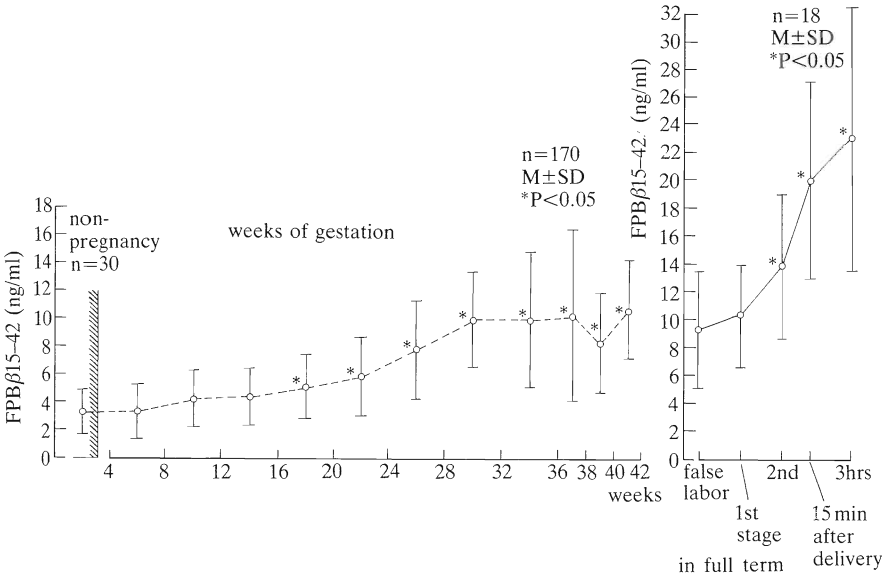

Fig. 2. Fluctuations of fibrinopeptide Bβ15–42 (FPBβ15–42) ng/ml during pregnancy, labor and puerperium

hours post-delivery (Figs. 1&2). In the cesarean cases, the FPA increased significantly during the operation and maintained the elevated level for 12 hours post operatively, (Fig. 3). The FPBβ15–42 also increased during the operation but it showed significant increase only at 3 and 6 hours postoperatively (Fig. 4). The FPA level in the uterine venous blood during operation showed a significant increase

Table 2. Plasma levels of fibrinopeptide A, fibrinopeptide Bβ15–42 and kallikrein-kinin system in cases of cesarean section delivery

	Not pregnant	Cesarean section									
		n	Before	During	Post-operation					During operation	
	n=30		operation	operation	3 hr.	6 hr.	12 hr.	24 hr.	48 hr.	Peripheral blood	Uterine blood
FPA (ng/ml)	1.0± 0.5	12	2.8± 1.7	* 26.3±17.8	* 11.0± 6.3	* 8.3± 5.3	* 5.9±3.6	4.3± 1.8	4.7± 1.9	26.3±17.8	* 89.1±63.3
FPBβ15–42 (ng/ml)	3.3± 1.8	12	9.7± 4.8	12.3± 5.3	* 23.9±14.6	* 15.4± 6.5	11.7± 5.8	11.7± 5.8	13.5± 7.6	12.3± 5.3	15.1± 5.7
Prekallikrein (%)	99.3±12.7	18	105.6±20.6	98.0±21.6	* 90.7±19.0	* 94.7±16.4	* 88.4±15.5	* 89.3±16.5	100.1±18.0	98.0±21.6	96.3±19.2
Kallikrein inhibitor (%)	98.2±14.8	18	81.4±24.4	70.7±27.9	* 63.8±31.6	* 62.3±29.8	* 61.2±31.0	78.4±30.8	92.5±36.2	70±27.9	65.1±27.7
HMW-kg (%)	82.6±26.6	20	78.7±24.8	71.9±23.6	68.3±20.5	70.9±15.3	70.6±16.0	67.9±18.4	86.8±28.5	71.9±23.6	73.3±20.0
Kinin (pg/ml)	10.8± 3.4	20	16.3± 5.9	20.5±14.1	20.0±15.6	* 24.4±14.7	20.1±11.1	14.2± 6.5	15.4± 7.0	20.5±14.1	21.3±15.0

Mean±SD *P<0.05 compared to full ferm pregnancy

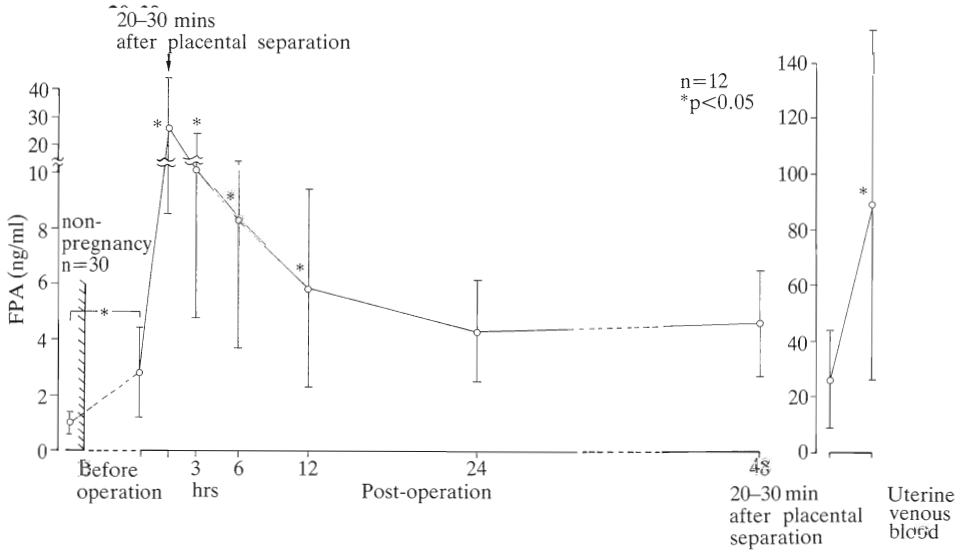

Fig. 3. Fluctuations of fibrinopeptide A (FPA) ng/ml in cases of cesarean section

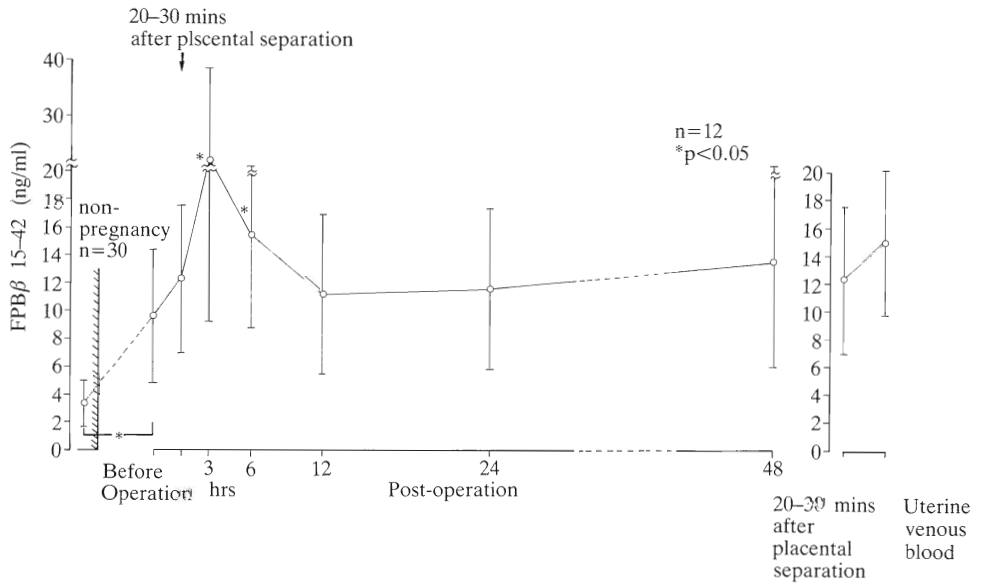

Fig. 4. Fluctuations of fibrinopeptide Bβ15–42 (FPBβ15–42) in cases of cesarean section

over the peripheral blood level, however, no significant difference between the FPBβ15–42 levels was found.

The level of HMW-kg increased during the second trimester of pregnancy and then gradually decreased through delivery with a significant decrease during labor in normal delivery (Fig. 5). In the cesarean section cases, the HMW-kg showed a slight decrease during and after the operation but no significant difference was found when compared with its level before the operation (Fig. 6). The level of kinin during normal pregnancy increased slight-

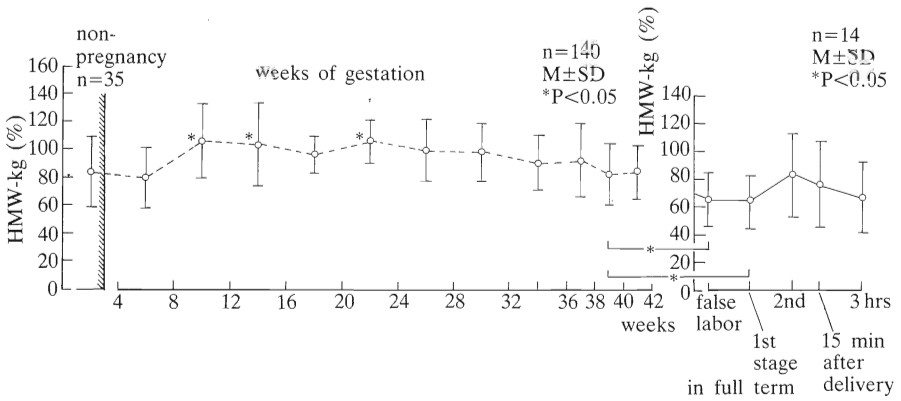

Fig. 5. Fluctuations of high molecular weight kininogen (HMW-kg)% during pregnancy, labor and puerperium

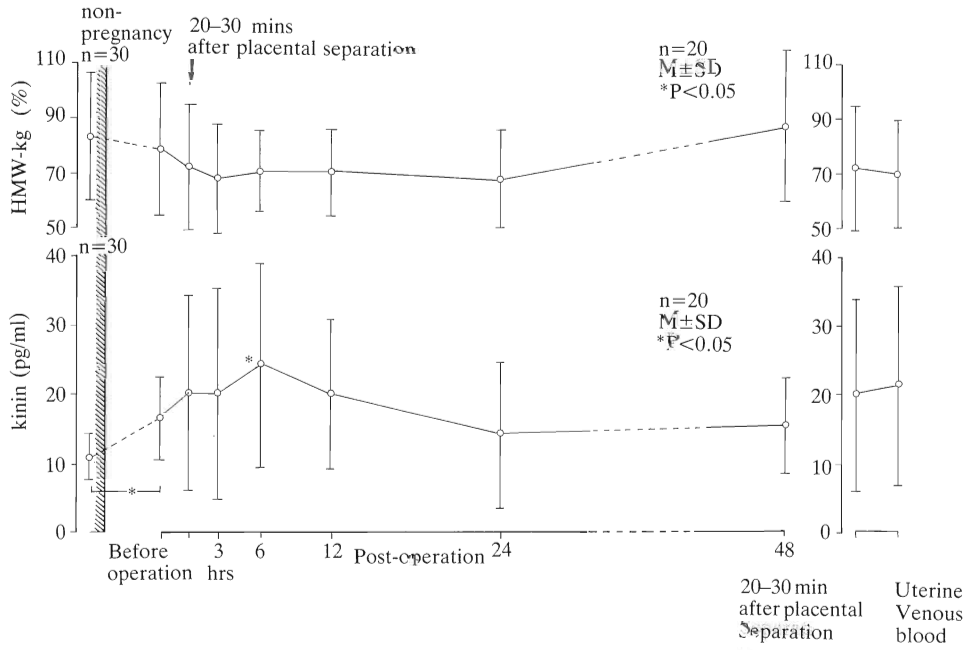

Fig. 6. Fluctuations of high molecular weight kininogen (HMW-kg)% and kinin pg/ml in cases of cesarean section

ly as pregnancy progressed, but there was no significant difference between the early and late stages of pregnancy, however, significant increase was found during normal delivery (Fig. 7). In cesarean delivery, the level of kinin increased significantly at 6 hours after the operation (Fig. 6). A significant decrease of the prekallikrein and the kallikrein inhibitor was found in the cesarean-section cases from 3 to 12 hours after the operation (Fig. 8).

Comments and Discussion

Several changes in the blood coagulation and fibrinolytic system are said to cause hypercoagulability during pregnancy and delivery[1–6]. Mutoh et al.[8] previously reported that during normal pregnancy, the

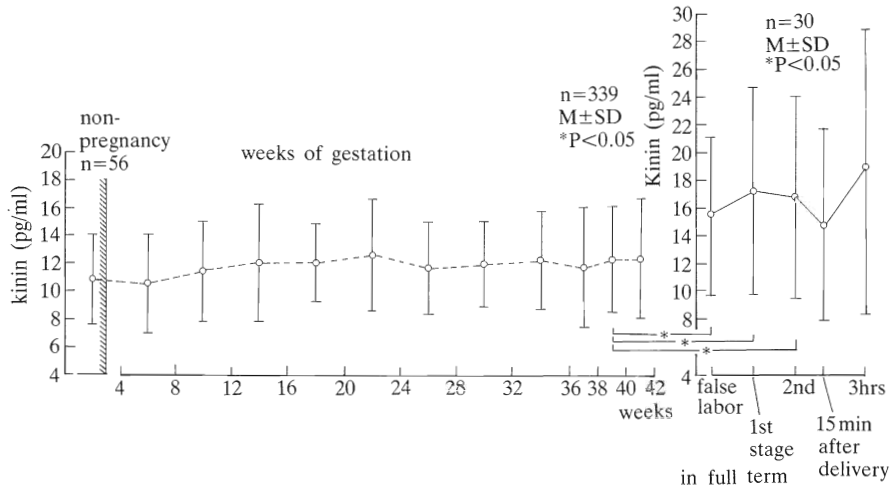

Fig. 7. Fluctuations of kinin pg/ml during pregnancy, labor and puerperium

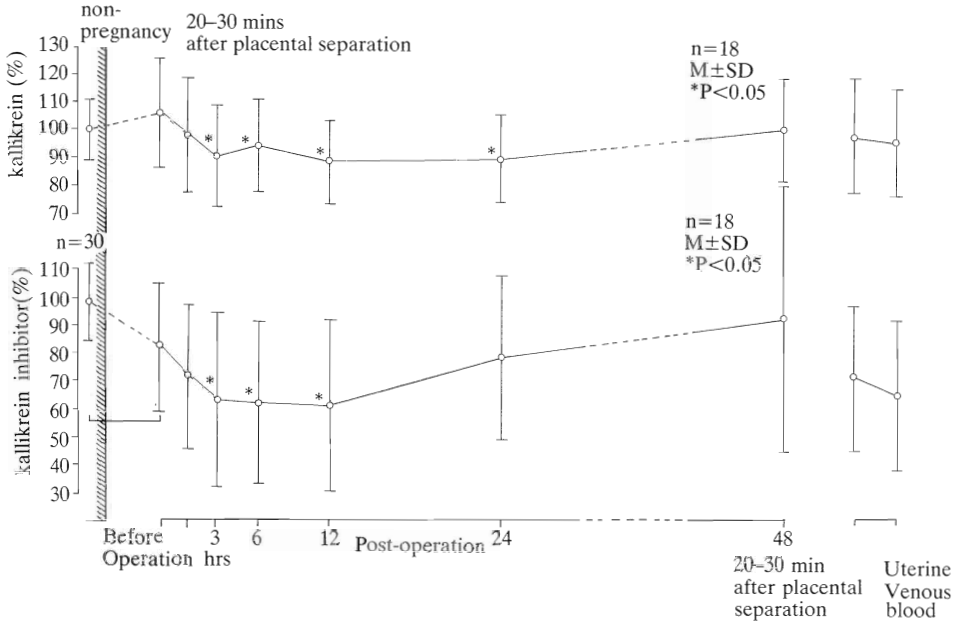

Fig. 8. Fluctuations of prekallikrein % and kallikrein inhibitors % in cases of cesarean section

activities of the intrinsic coagulation factors increased markedly after mid-term pregnancy and as pregnancy progressed to term, slight increase of the extrinsic factors was seen with the decrease of factors XIII and C_1-INA and increase of soluble fibrin monomer complex (SFMC) and FPD and that the fibrinolytic system was depressed as a whole during normal pregnancy and delivery. As for the cesarean section, our previous study[13] suggested that the hypercoagulable state and secondary hyperfibrinolysis were associated or interrelated during and after the cesarean section. In this study, the findings of increased fibrinopeptide A and fibrinopeptide Bβ15–42

indicated the activation of the thrombin and plasmin in the coagulation-fibrinolysis system, and the physiologic activation of these systems may contribute to a hypercoagulable state during pregnancy. When further stress and trauma were added during the cesarean section, the activities of thrombin and plasmin were prolonged and accompanied by secondary hyperfibrinolytic activities as witnessed by the maintenance of elevated blood levels of FPA and FPBβ15–42 for 6 to 12 hours after the operation (Figs. 3&4). The significant increase of FPA level in the uterine venous blood indicated increased blood coagulation activities locally during the cesarean section. Maki et al[14] reported that during normal onset of labor, the intrinsic coagulation factors XII and XI increased markedly resulting in the consumption and decrease of prekallikrein, and the kallikrein-like activity was pronouncedly activated; at the same time, the kallikrein inhibitors were activated and consumed and as a result, a sudden decrease of LMW-kg and HMW-kg was seen. The results of our present study, which showed a significant decrease of HMW-kg during normal labor and a decreasing tendency during and after the cesarean section, significant increase of kinin during normal delivery and at 6 hours postoperatively together with a significant decrease of prekallikrein and kallikrein inhibitor from 3 to 12 hours after the operation, suggested that the kallikrein-kinin system may be related to the onset of labor and post-delivery uterine contraction.

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