

J. Perinat. Med.  
27 (1999) 458–464

## Coagulation and fibrinolysis in viable mid-trimester pregnancies of normal, intrauterine growth retardation, chromosomal anomalies and hydrops fetalis and their eventual obstetric outcome

Stephen C. L. Koh, Chinnaiya Anandakumar, and Arijit Biswas

National University of Singapore, Department of Obstetrics and Gynecology, National University Hospital, Singapore

### 1 Introduction

Profound alterations in the coagulation and fibrinolytic systems occur during pregnancy and these changes enhanced a state of hypercoagulability in the Caucasians [6, 32] and ethnic Chinese women [19]. Fibrinolysis and its inhibitors, plasminogen activator inhibitor-1/2 (PAI-1/2) were also increased during pregnancy which reached maximum levels at the late third trimester or during labor [3, 8, 9] and in Asians [20, 26]. Low level intravascular coagulation has been suggested by some groups to occur from early normal pregnancy [19, 32] with an overall increased fibrinolysis [20, 32], whilst others found no such effect [24]. These changes in the coagulation and fibrinolysis are thought to be physiological which protect the mother from increased risk of bleeding during parturition [34]. The enhanced fibrinolysis reported during pregnancy, labor and the puerperium [7, 20] was countered by elevated PAI-1 and PAI-2 levels [8, 20, 30].

Hydrops fetalis is a state of excessive fluid accumulation in the extravascular compartment of the fetus, leading to widespread soft tissue edema and/or collection of fluid in the fetal body cavities. Hydrops fetalis is a non-specific pathological state resulting from etiological factors affecting the fetoplacental unit and its causes can be broadly divided into either immune or non-immune. It is often a lethal condition in association with homozygous  $\alpha$ -thalassaemia-1, cardiac de-

fects, chromosome abnormalities or of unknown causes. Hematologic disorders are seen in approximately 10% to 27% of the cases of nonimmune hydrops fetalis [5, 15, 28, 33] and anemia leading to heart failure, edema, ascites and anasarca, the final common finding [1]. Elevated PAI-1 antigen was seen in the fetal blood of fetal hydrops pregnancy associated with bad obstetric outcome [16]. Small for gestational-age fetuses are frequently seen in general obstetric practice and although remarkable improvements have been made in management in this group of conditions, much is still unknown. Lipid studies in intrauterine growth retardation (IUGR) pregnancies showed significantly lower levels of cholesterol and LDL-cholesterol [31] in contrast to high lipid levels that play a role in endothelial damage seen in preeclampsia. Depressed PAI-1 and PAI-2 were seen in the third trimester of IUGR pregnancies [4, 11] together with increased platelet activation [27]. PAI-2 depression could be due to diminished expression of mRNA in placenta [13]. Lower urokinase plasminogen activator (u-PA) level seen in IUGR pregnancy and in preeclampsia appears to reflect placental function, and both activity and concentration correlated with placental and fetal growth [25]. Anemia and associated thrombocytopenia have been reported in fetal triploidy [14].

Our study aims to determine whether the coagulation and fibrinolytic variables seen in viable mid-

trimester pregnancies diagnosed by ultrasound have any association with the eventual obstetric outcome of pregnancies with hydrops fetalis, chromosome anomalies, intrauterine growth retardation compared to uncomplicated pregnancy with good obstetric outcome.

## 2 Materials and methods

### 2.1 Subjects

The study received ethical approval from the Hospital Ethics Committee. A total of 71 pregnant women diagnosed by ultrasound to have uncomplicated normal pregnancy ( $n = 22$ ), intrauterine growth retardation (IUGR) pregnancy ( $n = 9$ ), pregnancy with non-immune hydrops fetalis ( $n = 23$ ) and fetal chromosomal anomalies ( $n = 17$ ) were studied for their coagulation, fibrinolytic and inhibitor levels with association on eventual obstetric outcome. The patients had given their informed consent to take part in the study and all were with known eventual obstetric outcome except for pregnancy with fetal chromosomal anomalies where eventual outcome could not be traced in ten pregnancies. Their age, gestation and eventual outcome with infant weight of good obstetric outcomes are shown in table I.

### 2.2 Blood collection

Nine parts of blood from a clean venepuncture were mixed with one part of 0.129 mol/L trisodium citrate (Merck) containing 0.21 mol/L HEPES (Sigma) in cold plastic tubes. The blood was spun immediately at 2000 g for about 15 minutes in a refrigerated centrifuge. For plasma tissue plasminogen activator (t-PA) activity, a 0.5 mL aliquot was acid-treated as described elsewhere [21]. Acid-treated and untreated plasma aliquots were stored at  $-70^{\circ}\text{C}$  until assayed.

### 2.3 Laboratory assays

The following assays were performed: citrate whole blood thrombelastography (TEG) [18] using the Thrombelastograph (Haemoscope, USA); plasma fibrinogen (Clauss technique) with an international standard from the National Institute of Biological Standards and Control (NIBSC), Hempstead, England; Factor VII (one stage assay) using deficient plasma from Pacific Haemostasis USA; antithrombin III (ATIII) activity (chromogenic substrate assay); plasminogen (chromogenic substrate assay); prothrombin fragment<sub>1+2</sub> (F<sub>1+2</sub>) (Behringwerke, Marburg, Germany); D-dimer (Stago, France); t-PA activity [21]; t-PA antigen (American Diagnostics Inc.,

**Table I.** Data of viable pregnancies diagnosed by ultrasound of normal, IUGR, hydrops fetalis, chromosomal anomalies and their known eventual obstetric outcome, mean (SD) and baby weight (95% CI) of good obstetric outcomes

n	Normal Pregnancy (good) 22	IUGR (good) 9	Hydrops Fetalis (good) 8	Hydrops Fetalis (bad) 15	Chromosome <sup>b</sup> anomalies 17
Age (years)	31.1 (5.2)	25.4 (3.7)	27.0 (4.6)	27.9 (3.8)	33.4 (4.2)
Gestation (weeks) @ blood sampling	23.8 (3.1)	26.7 (4.1)	26.7 (5.8)	25.8 (4.0)	23.5 (3.8)
Gestation (weeks) @ delivery/outcome	39.1 (1.2)	38.4 (2.1)	36.8 (1.3)	28.0 (1.1) <sup>a</sup>	25.9 (6.7) <sup>c</sup>
Baby weight (kg) with 95% C. I.	3.19 (0.4) 3.0–3.4	2.6 (0.6)* 2.2–3.1	3.05 (0.5) 2.6–3.5	– –	– –

\*  $p < .05$  compared to normal pregnancy; CI = confidence interval; (good)/(bad) = eventual outcome of pregnancies

<sup>a</sup> Barts hydrops pregnancy  $n = 7$ ; outcome TOP  $n = 7$ ; IUD/stillbirth  $n = 7$ ; preterm del 29/52  $n = 1$ .

<sup>b</sup> chromosome anomalies ( $\beta$ -Thalassaemia  $n = 1$ ; numerical  $n = 11$ ; structural  $n = 5$ ).

<sup>c</sup> (aborted  $n = 6$ ; term delivery  $n = 1$ ; unknown outcome  $n = 10$ ).

USA); urokinase plasminogen activator (u-PA) activity [23]; PAI-1 activity [22]; uPA antigen and PAI-1 antigen (Monozyme, Sweden); PAI-2 (Biopool, Sweden), proteins C and S were determined using Laurell's rocket method with international standards from NIBSC.

#### 2.4 Thromboelastography (TEG)

Computerized TEG (Haemoscope, Skokie, IL, USA), measures the blood coagulation kinetics in native or 'citrate' blood was performed as described elsewhere [18]. The following parameters were measured, r = reaction time, defined as the time for initial fibrin formation; k = coagulation time, defined as the interval from the end of the r value until the amplitude of the TEG tracing is 20 mm; mA = maximum amplitude is a reflection of absolute strength of the fibrin clot and depends on platelet function, fibrinogen, and coagulation factor levels.

#### 3 Statistical analysis

The Statistical Package for Social Sciences (SPSS) was used to perform statistical analysis. Mann-Whitney and non-parametric 2-independent t-test was used to compare the obstetric outcome of pregnancies with IUGR, hydrops fetalis and chromosomal anomalies; with uncomplicated normal pregnancy. A *p* value of < 0.05 was considered statistically significant.

#### 4 Results

The baby weights from pregnancies with eventual good obstetric outcome are shown in table I. Sig-

nificantly lower ( $P < 0.05$ ) baby weight was seen in IUGR pregnancy than in normal pregnancy. In hydrops fetalis pregnancy with eventual good obstetric outcome the baby weight was not significantly different when compared to infants born to mothers with uncomplicated normal pregnancy. The results of hemostatic parameters studied in pregnancies with IUGR, non-immune hydrops fetalis with good and bad obstetric outcomes, and in chromosomal anomalies are shown in tables I to IV.

#### 4.1 TEG, fibrinogen, Factor VII and prothrombin fragment<sub>1+2</sub> levels (table II)

*Thromboelastography.* There were no significant differences in reaction (r) or clotting times (k) in the 'other' pregnancies studied when compared with normal pregnancy except that clot elasticity (mA) was significantly greater ( $P < 0.05$ ) in IUGR pregnancy and hydrops fetalis pregnancy with bad obstetrics outcome.

No significant differences were seen for plasma fibrinogen and Factor VII levels in 'other' pregnancies studied compared to normal pregnancy. However, the mean levels were all above our non-pregnant normal reference range from our laboratory for fibrinogen  $3.01 \pm 0.5$  g/L and for Factor VII  $89 \pm 14$ %. Prothrombin fragment (F<sub>1+2</sub>) level was also above our laboratory normal reference range of mean  $0.85 \pm 0.5$  nmol/L and that only hydrops fetalis pregnancy with bad obstetric outcome showed significantly ( $P < 0.05$ ) elevated levels compared to normal pregnancy (mean 2.8 vs 2.1 nmol/L) respectively (table II).

**Table II.** Thromboelastography (TEG), fibrinogen, Factor VII, and F<sub>1+2</sub> levels in viable pregnancies diagnosed by ultrasound and known eventual obstetric outcome compared to normal pregnancy of good obstetric outcome mean (SD)

	TEG			Fibrinogen (g/L)	F VII (%)	F <sub>1+2</sub> (nmol/L)
	r (min)	k (min)	mA (mm)			
Normal Pregnancy	8.3 (1.4)	3.5 (0.8)	48.9 (3.9)	4.37 (0.8)	174 (29)	2.1 (1.1)
IUGR (good)	8.9 (1.2)	3.3 (0.6)	51.2 (3.0)*	4.76 (0.8)	187 (51)	2.5 (2.0)
H. fetalis (good)	8.0 (1.2)	2.6 (1.6)	50.6 (6.9)	4.54 (0.8)	202 (43)	2.6 (1.6)
H. fetalis (bad)	8.0 (1.2)	3.7 (1.9)	52.3 (5.6)*	4.43 (0.9)	185 (49)	2.8 (1.5)*
Chromosome anomalies	8.5 (1.7)	3.5 (1.1)	51.4 (5.4)	4.12 (0.7)	177 (60)	2.3 (1.7)

\*  $P < 0.05$ , r = reaction time, k = clotting time, mA = maximum amplitude.

#### 4.2 Plasminogen activators (t-PA, u-PA), plasminogen and D-dimer (table III)

There were no significant differences in t-PA (activity and antigen) and plasminogen levels in the 'complicated' pregnancies studied compared to normal pregnancy. The t-PA levels seen were within our laboratory normal reference mean of  $0.63 \pm 0.2$  IU/ml for activity and antigen mean of  $7.0 \pm 3.6$  ng/ml. The plasminogen levels seen were above our laboratory's normal reference mean of  $101 \pm 14.3\%$ . u-PA antigen was significantly elevated ( $P = 0.01$ ) together with D-dimer ( $P < 0.01$ ) levels in hydrops fetalis pregnancy with bad obstetric outcome, although increased mean trends in u-PA antigen and D-dimer levels were seen in hydrops fetalis pregnancy with good obstetric outcome. They however, did not reach statistical significance when compared to normal pregnancy probably due to the small number of cases studied. D-dimer and u-PA levels were not significantly different in IUGR and chromosomally abnormal pregnancies compared to normal pregnancy except that in fetal chromosomally abnormal pregnancy, decreased u-PA activity ( $P < 0.05$ ) was seen (table III). The normal non-pregnant level from our laboratory reference for u-PA activity was mean  $0.76 \pm 0.4$  IU/ml, and antigen  $1.10 \pm 0.5$  ng/ml; for D-dimer the level is less than 400 ng/ml of plasma.

#### 4.3 Plasminogen activator inhibitors (PAI-1, PAI-2), ATIII, proteins C and S (table IV)

No significant differences from normal pregnancy were seen in ATIII, proteins C and S and PAI-2

levels of the 'complicated' pregnancies studied. Elevated PAI-1 activity ( $P < 0.001$ ) and antigen ( $P < 0.01$ ) levels were seen in hydrops fetalis pregnancy with bad obstetric outcome and only elevated PAI-1 activity ( $P < 0.05$ ) seen hydrops fetalis pregnancy with good obstetric outcome whilst the other 'complicated' pregnancies showed no significant differences from normal pregnancy (table IV). Our laboratory's reference mean for PAI-1 activity was mean  $10.8 \pm 3.3$  AU/ml and antigen  $9.6 \pm 6.8$  ng/ml and PAI-2 was not detectable in non-pregnant women. The proteins C and S antigen levels studied were not significantly different from normal pregnancy and they were within our laboratory's reference mean of  $0.93 \pm 0.15$  IU/ml for protein C and mean  $0.85 \pm 0.13$  IU/ml for protein S antigen.

### 5 Discussion

The changes in coagulation and fibrinolysis during normal pregnancy progresses to a hypercoagulable state and by late pregnancy maximum haemostatic changes were seen [6, 9, 32]. Fibrinolysis and its inhibitors PAI-1 and PAI-2 also reached maximum levels at late stage of pregnancy or during labour [3, 8, 9, 20, 26]. The placenta is the main source of PAI-1 and PAI-2 during pregnancy [29] with a high concentration of u-PA [2]. In our study of late mid-term viable pregnancy, higher mean levels of fibrinogen, factor VII with enhanced prethrombin activation ( $F_{1+2}$ ) and increased clot elasticity (mA) than in non-pregnant reference level suggests a hypercoagulable state. However, in hydrops fetalis

**Table III.** Plasminogen activators (t-PA and u-PA), plasminogen and D-dimer levels in viable pregnancies diagnosed by ultrasound and known eventual obstetric outcome compared to normal pregnancy of good obstetric outcome mean (SD)

	t-PA		u-PA		Plasminogen (%)	D-dimer (ng/ml)
	act. (IU/ml)	ag (ng/ml)	act. (IU/ml)	ag (ng/ml)		
Normal pregnancy	0.41 (0.12)	7.4 (3.6)	0.74 (0.5)	0.86 (0.4)	152 (14)	621 (846)
IUGR (good)	0.44 (0.14)	8.4 (4.6)	0.67 (0.4)	1.00 (0.7)	145 (24)	701 (750)
H. fetalis (good)	0.43 (0.22)	11.4 (8.6)	0.61 (0.4)	1.40 (1.0)	155 (27)	1007 (1486)
H. fetalis	0.42 (0.18)	9.7 (5.7)	0.66 (0.3)	1.5 (0.9)**	156 (25)	1708 (1437)**
Chromo. anomalies	0.52 (0.29)	6.2 (2.8)	0.48 (0.1)*	0.76 (0.3)	153 (22)	409 (269)

\*  $P < 0.05$ ; \*\*  $P = 0.01$ . act = activity; ag = antigen.

**Table IV.** PAI-1 and PAI-2, ATIII and proteins C and S levels in viable pregnancies diagnosed by ultrasound and known eventual obstetric outcome compared to normal pregnancy of good obstetric outcome mean (SD)

	PAI-1		PAI-2	ATIII	Prot C	Prot S
	act (AU/ml)	ag (ng/ml)	(ng/ml)	%	(IU/ml)	(IU/ml)
Normal pregnancy	20.6 (6.4)	20.6 (6.2)	96.5 (35.3)	97 (9)	1.04 (0.2)	0.76 (0.17)
IUGR (good)	21.6 (10.0)	20.4 (8.3)	112.8 (47.2)	98 (13)	0.97 (0.2)	0.73 (0.14)
H. fetalis (good)	31.6 (11.6)*	23.3 (7.9)	117.3 (71.7)	98 (15)	1.17 (0.2)	0.76 (0.14)
H. fetalis (bad)	38.4 (16)***	32.1 (13)**	138.9 (76.1)	97 (15)	0.96 (0.2)	0.75 (0.15)
Chromosomal anomalies	24.6 (9.5)	21.6 (6.7)	98.6 (46.0)	95 (12)	0.97 (0.2)	0.75 (0.14)

\* P = < 0.05; \*\* P = 0.01; \*\*\* P = 0.001; act = activity, ag = antigen.

pregnancy, a significantly higher prothrombin activation and clot elasticity especially in bad obstetric outcome suggest an abnormally enhanced hypercoagulable state at this stage of late mid-trimester pregnancy. The significantly higher D-dimer, u-PA antigen and PAI-1 levels would also suggest an abnormally enhanced fibrinolytic/inhibitor state associated with bad obstetric outcome in hydrops fetalis pregnancy even though the systemic t-PA levels were not significantly raised. In hydrops fetalis pregnancy with eventual good obstetric outcome, higher mean PAI-1 activity was seen and similar trend with bad outcome in other haemostatic parameters studied was seen, but it did not reach statistical significance when compared with normal pregnancy probably due to the wide variations in results and the small number of subjects studied. No significant differences in the haemostatic parameters studied except for enhanced clot elasticity could be observed in IUGR pregnancy with eventual good obstetric outcome compared to normal pregnancy at this late mid-trimester pregnancy even though the infant weight at birth was significantly lower than observed in normal pregnancy. Similarly, no significant differences in haemostatic parameters studied could be seen in pregnancy with fetal chromosomal anomalies at this stage of pregnancy. Depressed PAI-2 levels in IUGR at third trimester have been reported [4, 11], and hyperfibrinolytic compensatory mechanisms was suggested [4]. Depressed u-PA antigen during labour was reported in IUGR [25] and appeared to correlate with placental and fetal growth. The higher mean levels of PAI-2 and u-PA antigen observed in IUGR and hydrops fetalis pregnancies in this

study would suggest that the placental function in synthesizing these proteins was not affected at least at this late mid-trimester pregnancy in contrast to preeclampsia where depressed levels were seen [10, 12, 17]. From these findings, it appears that in IUGR pregnancy the occurrence of onset of changes in placental growth and function associated with depressed fibrinolytic and inhibitor synthesis is evident at the third trimester or late pregnancy. Protein C which has anticoagulant properties and its cofactor protein S levels from the 'complicated' pregnancies were not significantly different from normal pregnancy at mid-trimester nor from our laboratory' reference for non-pregnant women except that lower level of mean protein S was seen during pregnancies.

In conclusion, a hypercoagulable state is present in late mid-trimester of normal, hydrops fetalis, IUGR including pregnancy with chromosomal anomalies. Further enhanced hypercoagulable and fibrinolytic/inhibitor state compared to normal pregnancy was associated with eventual bad obstetric outcome whilst PAI-1 activity was only further enhanced in those with eventual good outcome in hydrops fetalis pregnancies. In IUGR pregnancy, although higher clot elasticity (mA) and higher mean trends in coagulation and fibrinolytic parameters studied were seen, but they did not reach statistical significance similarly in pregnancy with chromosomal anomalies when compared to uncomplicated normal pregnancy. Our study suggests that in hydrops fetalis pregnancy, further enhanced prothrombin formation and fibrinolysis/inhibitor at late mid-trimester is associated with a poor obstetric outcome.

**Abstract**

A total of 71 pregnant women diagnosed by ultrasound to have viable fetus in late mid-trimester pregnancies of normal, IUGR, hydrops fetalis and chromosomal anomalies were studied for their coagulation, fibrinolytic and inhibitor levels with association on eventual obstetric outcome. A hypercoagulable state was observed in all the pregnancies studied. However, higher hypercoagulation evidenced by significantly raised prothrombin formation and clot elasticity together with higher levels of D-dimer, uPA antigen and PAI-1 than observed in normal pregnancy suggests a hyperfibrino-

lytic/inhibitor state in hydrops fetalis pregnancy associated with bad obstetric outcome. In IUGR pregnancy associated with good outcome further enhanced clot elasticity was seen whilst no significant differences were observed in pregnancy with chromosomal anomalies when compared to uncomplicated normal pregnancy. Our study suggests that in hydrops fetalis pregnancy, further enhanced prothrombin formation and hyperfibrinolysis/inhibitor at late mid-trimester is associated with a poor obstetric outcome.

**Key words:** Coagulation, fibrinolysis, obstetric outcome.

**Acknowledgements:** The study was made possible through the support from the National Medical Research Council Grant NMRC/0149/1996, RP 3960382N. We wish to express our thanks to Ms Chua SE, Mr Yuen WK and Ms Ng BL for their expert technical assistance and to the staff of the Antenatal Diagnostic Clinic for their assistance in blood samplings and recruitment of subjects into the study.

**References**

- [1] Arcasoy MO, PG Gallagher: Haematological disorders and nonimmune hydrops fetalis. *Semin Perinatol* 19 (1995) 502
- [2] Astedt B, I Lecander, T Brodin, A Lundblad, K Low: Purification of a specific placental plasminogen activator by monoclonal antibody and its complex formation with plasminogen activator. *Thromb Haemost* 53 (1985) 122
- [3] Bellart J, R Gilabert, J Fontcuberta, M Borell, RM Minalles, L Cabero: Fibrinolysis in normal pregnancy. *J Perinatal Med* 25 (1997) 368
- [4] Bellart J, R Gilabert, J Fontcuberta, E Carreras, RM Miralies, L Cabero: Coagulation and fibrinolytic parameters in normal pregnancy and in pregnancy complicated by intrauterine growth retardation. *Am J Perinatol* 15 (1998) 81
- [5] Benirschke K, P Kaufmann: Erythroblastosis fetalis and hydrops fetalis. In: *Pathology of the human placenta*. Springer-Verlag, New York NY 1995, p 421
- [6] Bonnar J: Haemostasis and coagulation disorders in pregnancy. In: Bloom AL, DP Thomas (eds): *Haemostasis and Thrombosis*. Churchill Livingstone Edinburgh 1987, pp 570
- [7] Bremer HA, EJP Brommer, HCS Wallenburg: Effects of labor and delivery on fibrinolysis. *Euro J Obst Gynecol* 55 (1994) 163
- [8] Bremme K, E Ostlund, I Almqvist, K Heinonen, M Blomback: Enhanced thrombin generation and fibrinolytic activity in normal pregnancy and the puerperium. *Obstet Gynecol* 80 (1992) 132
- [9] Cernea F, G Ricci, R Simeone, M Malisuno, S Alberico, S Guaschino: Coagulation and fibrinolytic changes in normal pregnancy. Increased levels of procoagulants and reduced levels of inhibitors during pregnancy induced hypercoagulable state, combined with a reactive fibrinolysis. *Euro J Obstet Gynecol & Reprod Biol* 73 (1997) 31
- [10] de Boer K, I Lecander I, JW ten Cate, JJJ Born, PE Treffers: Placental-type plasminogen activator inhibitor in preeclampsia. *Am J Obstet Gynecol* 158 (1988) 518
- [11] Estelles A, Gilabert J, Espana F, Aznar J, Galbis M: Fibrinolytic parameters in normotensive pregnancy with intrauterine fetal growth retardation and in severe preeclampsia. *Am J Obstet Gynecol* 165 (1991) 138
- [12] Estelles A, J Gilabert, J Aznar, DJ Loskutoff, RR Schleef: Changes in the plasma level of type-1 and type-2 plasminogen activator inhibitors in normal pregnancy and in patients with severe preeclampsia. *Blood* 74 (1989) 1332
- [13] Grancha S, A Estelles, J Gilabert, M Chirivello, F Espana, J Aznar: Decreased expression of PAI-2 mRNA and protein in pregnancies complicated with intrauterine growth retardation. *Thromb Haemost* 76 (1996) 761
- [14] Hohfeld P, F Forestier, Y Vial, JD Tissot: Hematological features of fetal triploidy: a report of 11 cases. *Biol Neonate* 72 (1997) 279
- [15] Holzgreve W, CJR Curry, MS Golbus MS, PW Callen, RD Filly, JC Smith: Investigation of non-immune hydrops fetalis. *Am J Obstet Gynecol* 150 (1984) 805
- [16] Koh SCL, C Anandakumar, A Biswas, SE Chua, WK Yuen, BL Ng, S Arulkumaran: Plasminogen

- activators and inhibitors in blood of fetus with good obstetric outcome compared to normal neonates and hydrops fetalis. *Fibrinolysis and Proteolysis* 12 suppl 12 (1998) Abstract 248
- [17] Koh SCL, C Anandakumar, S Montan, SS Ratnam: Plasminogen activators, plasminogen activator inhibitors and markers of intravascular coagulation in pre-eclampsia. *Gynecol Obstet Invest* 35 (1993) 214
- [18] Koh SCL, C Chew, OAC Viegas, BL Ng, SE Chua, R Yuen, M Choo, SS Ratnam: Thrombelastography in normal subjects and in various clinical states. *J Med Lab Scs* 7 (1993) 29
- [19] Koh SCL, SS Ratnam: Haemostatic trends in normal pregnancy in Chinese women. *J Obst Gynecol* 9 (1989) 271
- [20] Koh CLS, OAC Viegas, R Yuen, SE Chua, BL Ng, SS Ratnam: Plasminogen activators and inhibitors in normal late pregnancy, postpartum and in the postnatal period. *Int J Gynecol Obstet* 38 (1992) 9
- [21] Koh SCL, R Yuen, OAC Viegas, SE Chua, BL Ng, DK Sen, SS Ratnam: A plasmin generation method for the determination of tissue plasminogen activator (t-PA) activity in blood. *Immunol Cell Biol* 67 (1989) 197
- [22] Koh SCL, R Yuen, OAC Viegas, SE Chua, BL Ng, DK Sen, SS Ratnam: Plasma tissue plasminogen activator inhibitor (t-PAI) activity in normal subjects. *Med Sci Res* 17 (1989) 135
- [23] Koh SCL, R Yuen, OAC Viegas, SS Ratnam: Plasma urokinase activity and antigen levels in normal males, females and in late pregnancy. *Med Sci Res* 20 (1992) 601
- [24] Kruithoff EKO, C Tran-Thang, A Gudinchet A, J Hauert, G Nicoloso, C Genton, H Welti, F Bachmann: Fibrinolysis in pregnancy: a study of plasminogen activator inhibitors. *Blood* 69 (1987) 460
- [25] Lindoff C, B Astedt: Plasminogen activator of urokinase type and its inhibitor of placental type in hypertensive pregnancies and in uterine growth retardation; possible markers of placental function. *Am J Obstet Gynecol* 171 (1994) 60
- [26] Nakashima A, T Kobayashi, T Terao: Fibrinolysis during normal pregnancy and severe preeclampsia relationships between plasma levels of plasminogen activation and inhibition. *Gynecol Obstet Invest* 42 (1996) 95
- [27] Norris LA, BL Sheppard, G Burke, J Bonnar: Platelet activation in normotensive and hypertensive pregnancies complicated by intrauterine growth retardation. *Br J Obstet Gynaecol* 101 (1994) 209
- [28] Norton ME: Nonimmune hydrops fetalis. *Semin Perinatol* 18 (1994) 321
- [29] Philips M, AG Juul, S Thorsen, J Selner, J Zeuthen: Immunological relationship between fast-acting plasminogen activator inhibitor from plasma, blood, platelets and endothelial cells demonstrated with a monoclonal antibody against an inhibitor from placenta. *Thromb Haemost* 55 (1986) 213
- [30] Reith A, Booth NA, Moore NA, Cruickshank DJ, Bennett B: Plasminogen activator inhibitors (PAI-1 and PAI-2) in normal pregnancies, pre-eclampsia and hydatidiform mole. *Br J Obstet Gynaecol* 100 (1993) 370
- [31] Sattar N, IA Greer, PJ Galloway, CJ Packard, J Shephard, T Kelly, A Mathers: Lipid and lipoprotein concentrations in pregnancies complicated by intrauterine growth retardation. *J Clin Endocrinol Metab* 84 (1999) 128
- [32] Stirling Y, L Woolf, WRS North, MJ Seghatchian, TW Meade: Haemostasis in normal pregnancy. *Thromb Haemostas* 52 (1984) 176
- [33] Turkel SB: Conditions associated with nonimmune hydrops fetalis. *Clin Perinatol* 9 (1982) 613
- [34] Wallenburg HCS: Changes in the coagulation system and platelets in pregnancy-induced hypertension and preeclampsia. In: Sharp F, Symonds EM eds, *Hypertension in pregnancy*. Ithaca: Perinatology Press (1987) 227

Received July 5, 1999. Accepted August 19, 1999.

Stephen CL Koh  
 Department of Obstetrics and Gynaecology  
 National University Hospital  
 Lower Kent Ridge Road  
 Singapore 119704  
 Tel: +65 772 4114  
 Fax: +65 7794753