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ASSOCIATED WITH CASES OF
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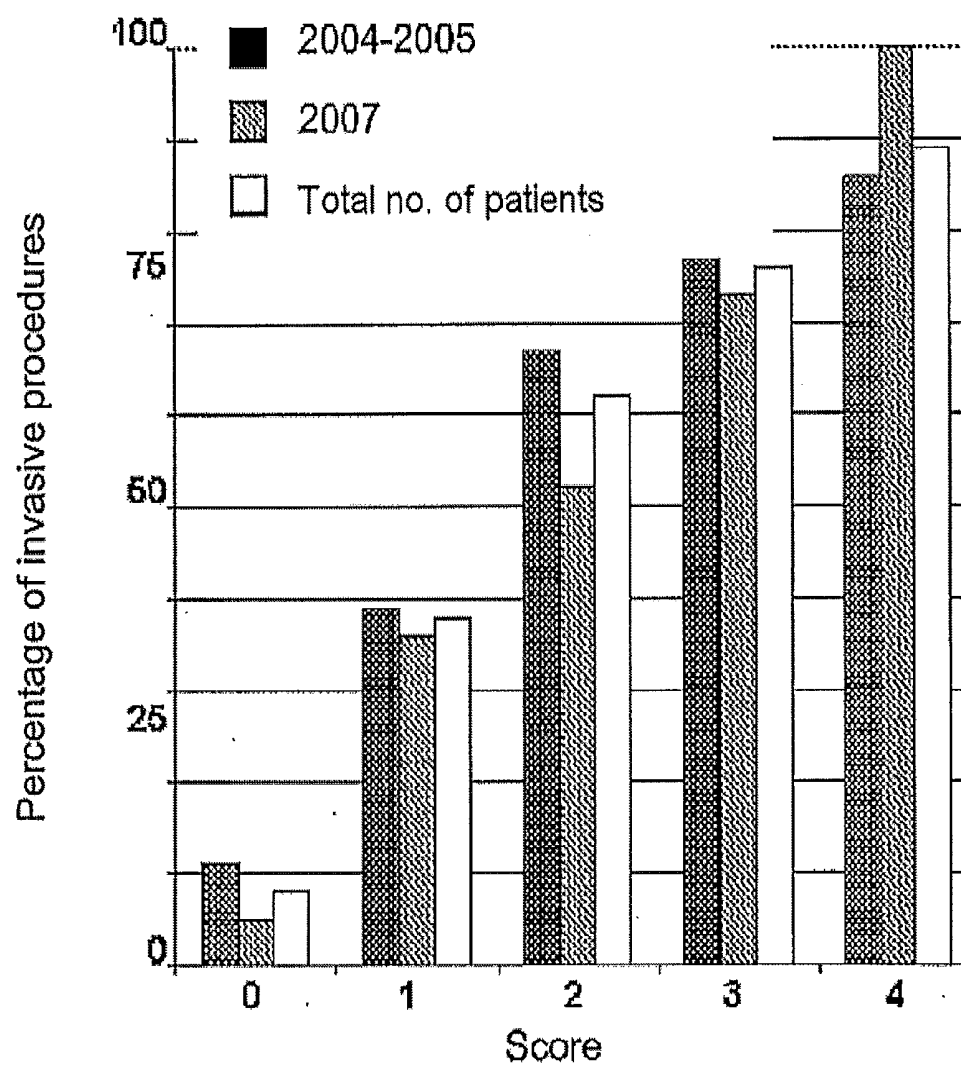
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USPC **600/371**(57) **ABSTRACT**

The present invention relates to an in vitro method of prognosis for the arrest of bleeding in a patient suffering from postpartum haemorrhage in the absence of an invasive procedure, comprising the following steps: (a) determining, using a biological sample from said patient, the plasma fibrinogen concentration, the blood troponin concentration and also the prothrombin time; (b) studying at least two clinical markers for said patient, selected from the group comprising heart rate and the presence of placenta abnormalities; (c) calculating a score Z according to the following equation: $Z=a+b+v+d+e$; where a is associated with the existence of placenta abnormalities in said patient, with a being 0 when no placenta abnormality is observed in said patient and a being 1 when one or more placenta abnormalities are observed in said patient; where b is associated with the heart rate of said patient, with b being 0 when the heart rate of said patient is less than or equal to 115 bpm (beats per minute) and b being 1 when the heart rate is greater than 115 bpm; where c is associated with the plasma fibrinogen concentration of said patient, with c being 0 when said concentration is greater than or equal to 2 g/L and c being 1 when said concentration is less than 2 g/L; where d is associated with the blood troponin concentration of said patient, with d being 0 when said concentration is less than the detection cut-off and d being 1 when said concentration is greater than or equal to the detection cut-off; where e is associated with the prothrombin time (PT) of said patient, with e being 0 when said prothrombin time is greater than or equal to 50% and e being 1 when said prothrombin time is less than 50%; where a score Z of greater than or equal to a value of 2 is an indication of the need to perform an invasive procedure in order to stop the bleeding in said patient suffering from postpartum haemorrhage.

**FIGURE 1**

NOVEL METHOD OF PROGNOSIS ASSOCIATED WITH CASES OF POSTPARTUM HEMORRHAGE

[0001] The present invention concerns a novel prognosis method associated with cases of postpartum haemorrhage.

[0002] Post-partum haemorrhage, which is defined as the loss of more 500 ml of blood after giving birth, is still seen in nearly 18% of births. The annual incidence of postpartum haemorrhage is therefore 14 million cases across the world; these being the cause of 124,000 maternal deaths. In France, the annual incidence of these haemorrhages is 70,000 to 80,000 cases which are responsible for nearly 250 deaths. In this respect, a French report explains that nearly 75% of these deaths involve failed management regarding recommended practice, notably integrating the time before transfusion, haemostatic procedure, etc.

[0003] However, since the causes of these haemorrhages are multiple, it is difficult at the present time to define a management protocol which could limit mortality arising after postpartum haemorrhage.

[0004] There is therefore an urgent need to develop a predictive test enabling practitioners to provide better management of patients suffering from post-partum haemorrhage.

[0005] After an exhaustive analysis of different cohorts of parturients who had suffered postpartum haemorrhage, the inventors have evidenced the existence of different risk factors on which they have developed a score allowing prediction of the need to carry out invasive procedure to stop bleeding.

[0006] Therefore, a first object of the invention is an in vitro method for the prognosis of halted bleeding in a patient suffering from postpartum haemorrhage without any invasive procedure, which comprises the following steps:

[0007] a) determining, from a biological sample of said patient, the plasma fibrinogen concentration, blood troponin concentration and prothrombin time;

[0008] b) examining at least two clinical markers of said patient, chosen from the group consisting of heart rate and the presence of placental anomalies;

[0009] c) calculating a score Z using the following formula: $Z=a+b+c+d+e$,

[0010] i) where a is associated with the existence of placental anomalies in said patient, with a having a value of 0 when no anomaly of placentation is observed in said patient, and a having a value of 1 when one or more placentation anomalies are observed in said patient;

[0011] ii) where b is associated with the heart rate of said patient, with b having a value of 0 when said patient's heart rate is less than or equal to 115 bpm (beats per minute) and b has a value of 1 when the heart rate is higher than 115 bpm;

[0012] iii) where c is associated with the plasmatic fibrinogen concentration of said patient, with c having a value of 0 when said level is equal to or higher than 2 g/L, and with c having a value of 1 when said level is lower than 2 g/L;

[0013] iv) where d is associated with the blood troponin concentration of said patient, d having a value of 0 if said concentration is lower than the detection threshold, and with d having a value of 1 when said concentration is higher than or equal to this same detection threshold;

[0014] v) where e is associated with the prothrombin time (PT) of said patient, e having a value of 0 if said prothrombin time is higher than or equal to 50%, and e having a value of 1 if said prothrombin time is less than 50%;

wherein a Z score of 2 or more than 2 is indicative of the necessity to carry out invasive procedure to stop bleeding in said patient suffering from postpartum haemorrhage.

[0015] The inventors have effectively evidenced that a score of 2 or higher is associated with a probability of more than 70% of the need for invasive procedure. More specifically, the inventors have evidenced that a score of 2 is associated with a probability of nearly 50% of the need for invasive procedure, a score of 3 is associated with a probability of more than 75% and finally a score of 4 is associated with a probability of the order 90% of the need for invasive procedure.

[0016] Finally, the method developed by the inventors allows the simple and highly sensitive determining of those patients suffering from post-partum haemorrhage who will need invasive procedure to stop bleeding, so that it is possible to envisage patient management that is prompt and best adapted.

[0017] Preferably, by "biological sample" is meant a blood sample.

[0018] By "fibrinogen" or "I factor" is meant a glycoprotein of blood plasma which converts to fibrin under the action of thrombin when the blood coagulates. This glycoprotein is soluble and has a normal concentration in human plasma of between 1.8 and 4.0 g/L. The plasma concentration of fibrinogen can be simply determined using measurement methods well known to the person skilled in the art. As an example of method for measuring fibrinogen concentration, mention may be made of the ELISA method such as used in the STA FIBRINOGEN kit (DIAGNOSTICA STAGO).

[0019] By "troponin" is meant a protein complex acting in the sensitization of muscle cells to calcium.

[0020] By "detection threshold" and for troponin, is meant a concentration higher than the detectable concentration for the method used. For example, by detection threshold is generally meant a value of 1 pg/L, preferably 10 pg/L and further preferably 0.02 ng/L.

[0021] Therefore, d has a value of 0 when said concentration is lower than 1 pg/L, preferably lower than 10 pg/L, and most preferably lower than 0.02 ng/L.

[0022] Preferably, the troponin is troponin I.

[0023] BY "Troponin I" or "TnI" is meant the protein subunit responsible for the inhibition of binding between myosin and actin (by masking the actin site used for binding with myosin).

[0024] Further preferably, said troponin I is cardiac troponin I (SEQ ID NO:1) which has an inhibitory function allowing the triggering of muscle relaxation.

[0025] Troponin, and notably troponin I, is normally not found in the blood, detection thereof in the blood being the result of stress, and its normal blood level is to be considered zero. The detection of troponin or troponin I can be performed using methods well known to the person skilled in the art. For example, particular mention may be made of immunofluorescence using the STAT Troponin-I kit (Architect 1.2000SR Abbott), TROPONIN I ELISA kit (CALBIOTECH), or CLEARVIEW TROPONIN I (INVERNESS MEDICAL INTERNATIONAL).

[0026] By "prothrombin time" or "TP", sometimes called "Quick time" reference is made to the coagulation time of a citrated blood plasma in the presence of an extract of human, animal or synthetic tissue called thromboplastin, cytozyme or thrombokinase which comprises a set of enzymes required for blood coagulation and allows the conversion of prothrombin to thrombin. More specifically, Quick time corresponds to this measured coagulation time expressed in seconds relative to the time obtained for a control plasma (the mean of around fifty normal patients) and the prothrombin time corresponds to a percentage value obtained by plotting the Quick time obtained for the plasma being tested on Thivolle's straight line (obtained by testing successive dilutions of a normal control plasma). For example, the prothrombin time of normal plasma by definition is 100%, that of normal plasma diluted to one half is 50%, and this prothrombin time normally lies between 70 and 100%.

[0027] This prothrombin time can be measured simply using very numerous kits or apparatus available on the market such as the kits STA NEOPLASTINE (DIAGNOSTICA STAGO) or IMMEDIA™ PT System (FARALLON MEDICAL).

[0028] However, this prothrombin level has the major defect of varying according to the reagent used, which is why it is preferred to use the INR (International Normalized Ratio) for the comparison of repeated measurements in one same patient. The INR uses no unit but takes into account the sensitivity of the thromboplastin reagent according to an internationally determined index. For example, a prothrombin time of less than 50% corresponds to an INR score of more than 1.6 (for PT measured using the STA NEOPLASTINE kit (DIAGNOSTICA STAGO)).

[0029] By "placentation anomalies" is meant an anomaly of placenta insertion. As examples of placentation anomalies mention may be made of placenta praevia, placenta accreta, placenta increta and placenta percreta.

[0030] Placenta praevia is characterized by low insertion of the placenta (lower segment of the uterus) which therefore partly or fully obstructs the natural birth canal, amounting to a mechanical obstacle to giving birth via vaginal route.

[0031] With placenta accreta, the placenta pathologically adheres to the wall of the uterine cavity, in this anomaly, the decidua disappears and the trophoblastic villi attach themselves directly onto the muscle layer of the uterine wall (myometrium). Depending upon the extent of penetration of the placental trophoblastic villi into the myometrium, three degrees of seriousness are described:

[0032] placenta accreta: the invasion of the trophoblastic villi is limited to the surface layer of the myometrium;

[0033] placenta increta: the trophoblastic villi penetrate into the thickness of the myometrium;

[0034] placenta percreta: the trophoblastic villi pass through the entirety of the thickness of the myometrium to reach the serosa and even neighbouring organs (the bladder in particular).

[0035] By "invasive procedure" is meant haemostatic surgery or invasive arterial embolisation.

[0036] As an example of haemostatic surgery, mention may be made of hysterectomy, vascular ligation and/or intra-abdominal packing. Said operations for haemostatic surgery are notably described in the article by SERGENT et al (*Ann. Chir.*, vol. 131(4), P. 236-43, 2006).

[0037] The method according to the invention, in parallel to calculating the score, may comprise a step to determine other

biological parameters such as the haemoglobin count, these parameters not being used for calculation of the score.

[0038] The present invention will now be described in more detail with the help of examples illustrating the invention but which in no way limit the scope thereof.

EXAMPLES

1) Determining a Postpartum Haemorrhage Score to Predict the Need for Invasive Procedure

[0039] A cohort of 257 patients of mean age 31 years (28-35) suffering from postpartum haemorrhage was chosen, these patients having been admitted between Jan. 1, 2004 and Dec. 31, 2005 to hospital Lariboisière (Paris, France). Among these 257 patients, had already been initially admitted to hospital Lariboisière and the 227 other patients were admitted after transfer from another hospital centre after different treatments administered to reduce bleeding had failed to prove effective. The mean transfer time was 4.8 hours (3.4-7.2) during which transfer the majority of parturients (87%) were given continuous infusions of sulprostone. More specifically, 12 had already undergone a hysterectomy and 11 vessel ligation.

[0040] On their admission to the unit, the patients were taken in charge with monitoring and correction of immediate hemodynamic disorders that were life-threatening. The persistence and intensity of bleeding from the vagina and/or peritoneum were assessed by physical examination together with ultrasound investigation.

[0041] On admission, the parturients showed severe signs, with haemoglobin levels of 9.2 g/L and hematocrit levels of 27% despite transfusion of an average of two globular concentrates and one fresh frozen plasma before admission. The parturients also showed other haemorrhagic signs including tachycardia (mean heart rate of 107 bpm), coagulopathy (mean prothrombin time (PT) of 67%) and thrombocytopenia (mean number of platelets of 118,000 per mm³). The SAPS II score (Simplified Acute Physiology Score) was 18 in the 257 patients.

[0042] These first analyses showed that the main cause of postpartum haemorrhage was uterine atony (69%), lesions of the genital tract (22%) and finally placental anomalies (8%).

[0043] In relation to the results obtained, two therapeutic options could be envisaged: 1) invasive procedure to control genital bleeding including i) surgical haemostasis or ii) angiography with uterine embolisation; and 2) if neither of the above was immediately indicated since bleeding had either stopped or was minimal, the parturients were kept under observation.

[0044] After initial evaluation, 110 parturients underwent haemostatic invasive procedures due to persistent bleeding, after which the parturients were kept in the intensive care or intermediate care unit.

[0045] These procedures included 85 arterial embolisations alone (mostly uterine arteries), 14 haemostatic surgical procedures alone, and 11 embolisations and surgery combined. Haemostatic surgery (n=25) included hysterectomies, vessel ligatures and peritoneal dressings; whether or not combined. More specifically, the arterial embolisations were performed 1.9 hours (1.2-2.5) after admission, and the invasive procedures were performed 2.1 hours (1.4-4.6) after admission.

[0046] For the remainder of this analysis, the cohort of 257 patients was sub-divided into sub-groups depending on

whether the patient had or had not undergone invasive procedure, invasive procedure (IP) being defined as haemostatic surgery (hysterectomy and/or vessel ligation and/or intra-abdominal packing) and/or uterine arterial embolisation. Therefore the 257 patients were subdivided into an “IP” group for those patients requiring IP, and a “medical monitoring” group (MM) which included patients who had not undergone any of the above-mentioned procedures.

[0047] For the 110 parturients in the IP group, two deaths were recorded, and the mean stay time for the other parturients in this group was 3.2 days (2.3-6.2), bleeding having been halted in all parturients and no re-admission to hospital being observed.

[0048] For the 147 parturients in the MM group, bleeding was considered as low either on admission or thereafter. There was no mortality in this group and the mean hospital stay for these patients was 0.9 day (0.65-2.1) with no subsequent readmission to hospital.

[0049] The precise characteristics of these two sub-groups compared with the cohort as a whole are detailed in following Table I.

TABLE I

		Cohort (n = 257)	MM sub-group	IP sub-group
Arterial embolisation (n = 96)	Single session	96 (37%)	—	96 (37%)
	Need for 2 nd session	7 (2.7%)	—	7 (2.7%)
Haemostatic surgery (n = 25)	Hysterectomy	7 (2.8%)	—	7 (2.8%)
	Intra-abdominal packing	17 (6.7%)	—	17 (6.7%)
	Vessel ligation	6 (2.4%)	—	6 (2.4%)
Severity and prognosis	SAPS II	18 (12-24)	15 (12-21)	22 (16.5-32)
	APACHE II	10 (6-13)	7 (6-11)	12 (8-16)
	Prognosis intensive care	37 (14.4%)	6 (4%)	31 (28%)
	Stay time (days)	1.97 (0.8-4.0)	0.94 (0.65-2.1)	3.22 (2.3-6.17)
	Mortality	2 (0.8%)	0 (0%)	2 (1.8%)

[0050] More specifically, the different patient parameters respectively collected prior to admission and at the time of admission are respectively given in following Tables II and III.

TABLE II

	Total (n = 257)	MM Group (n = 147)	IP Group (n = 110)	p value
Age	31 [29-35]	31 [27-35]	32 [30-36]	0.019
Obstetric parameters				
Primiparas	109 (46)	49	41	0.23
Primigravidas	85 (35)	39	29	0.51
Prior postpartum haemorrhage	8 (3)	4	2	0.48
Uterine fibroma	12 (5)	9 (6)	3 (3)	0.37
Scarred uterus	30 (12)	14 (8)	16 (16)	0.07
Toxaemia	30 (12)	18 (12)	12 (12)	0.92
Term (weeks)	39 [37-40]	39 [38-40]	39 [37-40]	0.042
Twin pregnancy	15 (6)	7 (6)	8 (7)	1
Birth at university hospital	57 (22)	25 (15)	32 (32)	0.0016
Delivery details				
Induced birth	49 (20)	37 (25)	12 (13)	0.034
Vaginal birth	175 (70)	110 (75)	65 (65)	0.21

TABLE II-continued

	Total (n = 257)	MM Group (n = 147)	IP Group (n = 110)	p value
Labour (hours)	5 [4-8]	6 [4-8]	4 [2-6]	0.016
Use of instruments	51 (21)	33 (22)	18 (19)	0.63
Manual removal of the placenta	124 (49)	71 (48)	53 (53)	0.31
Uterine examination	174 (70)	106 (72)	68 (68)	0.57
Obstetrical anaesthesia				0.35
General anaesthesia	27 (10)	13 (9)	14 (14)	
Epidural anaesthesia	162 (65)	98 (66)	64 (62)	
Spinal anaesthesia	30 (12)	18 (12)	12 (13)	
No anaesthesia	31 (13)	20 (14)	11 (11)	
Causes of haemorrhage				0.0034
Primary uterine atony	178 (69)	109 (74)	69 (61)	
Genital lesion	56 (22)	34 (23)	22 (20)	
Placental anomaly	20 (8)	4 (3)	16 (14)	
Uterine rupture	3 (1)	0 (0)	3 (3)	

TABLE II-continued

	Total (n = 257)	MM Group (n = 147)	IP Group (n = 110)	p value
Surgical procedure before transfer				
Vaginal examination (retractor)	90 (36)	61 (41)	29 (30)	0.11
Hysterectomy	12 (5)	4 (3)	8 (8)	0.079
Intraabdominal packing	5 (2)	0 (0)	5 (5)	0.012
Vessel ligation	11 (4)	7 (5)	4 (4)	1
Medical monitoring before admission				
Sulprostone infusion	217 (87)	131 (89)	86 (85)	0.44
Catecholamine	5 (2)	0 (0)	5 (5)	0.011
Mechanical ventilation	35 (14)	13 (9)	22 (20)	0.028
Globular concentrate	1.8 ± 3.2	1.2 ± 2.0	2.8 ± 4.1	0.00042
Fresh frozen plasma	1.0 ± 2.4	0.6 ± 1.7	1.6 ± 3.1	0.0026
UCP	0.2 ± 1.3	0.1 ± 0.4	0.4 ± 1.9	0.11
Time between birth and admission (hours)	5 [3-7]	5 [4-7]	4 [3-7]	
Transport time (hours)	0.5 [0.2-0.7]	0.5 [0.2-0.7]	0.5 [0.2-0.7]	1

TABLE III

	Total (n = 257)	MM Group (n = 147)	IP Group (n = 110)	p value
Haemodynamic status				
SAP (Systolic arterial pressure) (mmHg)	110 [95-120]	110 [100-120]	100 [87-115]	0.00069
DAP (diastolic arterial pressure) (mmHg)	55 [50-60]	60 [50-65]	50 [45-60]	0.00084
HR (heart rate) (bpm)	105 [90-120]	100 [90-115]	115 [100-130]	1.6 ^e -05
Biological values				
pH	7.42 [7.37-7.44]	7.43 [7.4-7.45]	7.39 [7.32-7.43]	1.9 ^e -06
PaCO ₂ (mmHg)	32 [29-36]	32 [29-35]	33 [29.25-38]	0.1
PaO ₂ (mmHg)	161 [110-220.8]	138 [104-187]	195 [144-247]	9.1 ^e -06
Bicarbonate (mmol/L)	22 [21-24]	23 [22-24]	22 [20-23]	3.8 ^e -05
Proteins (g/L)	42 [37-49]	45 [40-51]	38 [32.5-43]	1.7 ^e -10
Creatinine (μmol/L)	58 [50-69]	57.5 [50.75-67.25]	59 [48.5-70.5]	0.66
Lactate (mmol/L)	2.13 [1.56-2.76]	1.91 [1.39-2.5]	2.5 [1.92-3.73]	6.8 ^e -07
AST (IU/mL)	22 [18-31]	23 [19.25-30]	21 [16-31]	0.094
ALT (IU/mL)	13 [10-17]	12 [10-16]	13 [10-18]	0.13
Troponin I (ng/mL)	0 [0-0.2]	0 [0-0.03]	0.06 [0-0.4]	1.6 ^e -07
Bilirubine (mmol/L)	7 [4-12]	7 [4-11]	8 [5-15]	0.17
Hb (g/dL)	9.2 [7.9-10.3]	9.5 [8.2-10.6]	8.7 [7.0-9.9]	0.0013
Hematocrit (%)	27 [23-30]	27 [24-31]	25 [20-30]	0.00064
Platelets (/mm ³)	118,000 [80,250-154,000]	130,500 [97,750-161,200]	92,500 [63,750-133,000]	4.5 ^e -05
PT (%)	69 [55-79]	73 [64-85]	58.5 [38-73]	8.7 ^e -09
Fibrinogen (g/L)	2.34 [1.55-3.12]	2.65 [2.08-3.46]	1.8 [1.09-2.52]	2.9 ^e -10
Factor V (%)	49 [31-61]	52 [39-66]	41 [23-56]	0.00057

[0051] The results show that, among the demographic and obstetric parameters collected prior to admission of the patients, very few differences were able to be identified between the IP and MM groups (see Table II).

[0052] Among the significant identified parameters, mention may be made of older patients, shortened term, shorter labour time, more frequent use of induced labour, weaker primary uterine atony and more placental anomalies (placenta praevia, placenta accreta and placenta percreta) in the patients of the IP group compared with the MM group. On the other hand, major differences could be observed in hemodynamic and biological measurements between the IP and MM groups on admission (see Tables II and III). The patients in the IP group showed unstable hemodynamic status with low SAP and DAP, high heart rate, low haemoglobin level, high level of plasma troponin I and metabolic acidosis despite major transfusion of red blood cells and stronger administration of catecholamine. Coagulopathy was also higher in the IP group with a low number of platelets, low PT, low level of factor V

and of fibrinogen levels even though more patients had been transfused in the IP group than in the MM group.

[0053] With a view to identifying pertinent parameters to determine a predictive model for invasive procedure, these different parameters were further analyzed. Since the objective of the study was to determine at least the necessity of embolisation, intra-abdominal packing, hysterectomy or vessel ligation, a marginal association was determined between variables taken alone and prognosis using a WILCOXON test for quantitative variables and an exact FISCHER test.

[0054] For this purpose, multiple logistic regression was used to determine a set of variables independently associated with each prognosis. The variables associated with invasive procedure at a level of 0.15 and with less than 5% of missing data were taken into consideration in the multiple model. For internal clinical validity, the continuous covariables were categorised, notably systolic arterial pressure (SAP) <90 mmHg, diastolic arterial pressure (DAP) <55 mmHg, heart rate (HR) >115 beats per minute (bpm), prothrombin time (PT) <50%, fibrinogen level <2 g/L and troponin I level detectable or non-detectable.

[0055] Finally, multivariate analysis allowed the identification of 5 independent factors predictive of the IP group, which factors could be identified on admission of the patients. These factors are the following:

[0056] 1) placental anomalies (OR: 7.05[2.26-22.03], p=0.0007)

[0057] 2) Heart rate (HR)>115 bpm (OR: 2.18[1.03-4.62], p=0.04)

[0058] 3) Prothrombin time <50% (OR: 3.55[1.38-9.17], p=0.008)

[0059] 4) Fibrinogen <2 g/L (OR: 2.75[1.51-4.95], p=0.005)

[0060] 5) Detectable troponin I level (OR: 2.73[1.51-4.95], p=0.0009).

[0061] Having regard to these factors, it was possible to develop a predictive score for a given patient, a value of 1 being assigned in this score for each of the above if it was observed in this patient. For a given patient, and in relation to the factors identified in this patient, a score can therefore be determined which will have a value of between 0 and 5 depending on whether or not one or more of these above-described factors are observed.

[0062] It emerged from the results obtained that a patient having a score of at least two or more carried a risk of more than 70% that invasive procedure would be necessary to stop bleeding subsequent to a postpartum haemorrhage.

2) Validation of the Predictive Model

[0063] To do so, the predictive model was tested in a new cohort of 150 patients suffering from postpartum haemorrhage and admitted throughout the year 2007. The different parameters measured on admission in this new cohort compared with the previous cohort are given in Table IV.

TABLE IV

	2004/2005 Cohort (n = 257)	2007 Cohort
OBSTETRICAL DETAILS		
Age	31 (29-35)	32 (28-36)
Primiparas	109 (46)	67 (44)
Primigravidas	85 (35)	56 (37)
Toxaemia	30 (12)	15 (11)
Transfer from university hospital	57 (22)	51 (34)
Twin pregnancy	15 (6)	8 (5)
Term (weeks)	39 (37-40)	39 (38-40)
Delivery details		
Vaginal delivery	175 (70)	83 (56)
Use of instruments	51 (21)	20 (14)
Uterine examination	174 (70)	83 (55)
Cause of haemorrhage		
Primary uterine atony	178 (69)	110 (73)
Genital tract lesion	56 (22)	28 (19)
Placental anomaly	20 (8)	11 (7)
Uterine rupture	3 (1)	1 (1)

TABLE IV-continued

	2004/2005 Cohort (n = 257)	2007 Cohort
MANAGEMENT BEFORE TRANSFER		
Time before transfer	5 (3-7)	4.8 (3.4-7.2)
Surgery before transfer		
Examination with vaginal retractor	90 (36)	75 (50)
Hysterectomy	12 (5)	4 (3)
Vessel ligation	11 (4)	8 (5)
Medical treatment		
Sulprostone infusion	217 (87)	141 (94)
Mechanical ventilation	35 (14)	15 (10)
Globular concentrate	1.8 ± 3.2	2.1 ± 2.8
Fresh frozen plasma	1.0 ± 2.4	1.1 ± 2.3
VALUES ON ADMISSION		
Haemodynamic		
SAP (mmHg)	110 (95-120)	120 (110-132)
DAP (mmHg)	55 (50-60)	70 (60-78)
HR (bpm)	105 (90-120)	100 (80-110)
Biological values		
Troponin I (ng/mL)	0 (0-0.2)	0 (0-0.4)
Hb (g/dL)	9.2 (7.9-10.3)	9.0 (7.5-10.3)
Platelets (per mm ³)	118,000 (80,250-154,000)	130,000 (92,000-160,000)
PT (%)	69 (55-79)	67 (58-76)
Fibrinogen (g/L)	2.34 (1.55-3.12)	2.7 (1.91-3.28)
PATIENT MANAGEMENT AT THE CENTRE		
SAPS-2	18 (12-24)	13 (9.5-20)
Arterial embolisation	96 (37%)	37 (25%)
Second arterial embolisation	7 (2.7%)	2 (2%)
Haemostatic surgery		
Hysterectomy	7 (2.8)	2 (1)
Vessel ligation	6 (2.4)	2 (1)
Stay in intensive care	37 (14.4%)	10 (7%)
Mortality	2 (0.8%)	0 (0%)

[0064] The results showed that the characteristics of the 2007 cohort are similar to those of the preceding cohort, with a greater number of vaginal retractor examinations however and fewer invasive procedures than in the preceding cohort.

[0065] The previously developed score was used in this new cohort.

[0066] FIG. 1 shows the results of the score such as described in the foregoing for the 2004/2005 cohort, the 2007 cohort and for all patients taken together with respect to the risk of invasive procedure.

[0067] Finally, the results obtained gave confirmation of the high specificity of the score such as developed, as a tool predictive of the necessity for invasive procedure to stop bleeding subsequent to postpartum haemorrhage (see FIG. 1).

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 1

<210> SEQ ID NO 1

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<212> TYPE: PRT
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          20          25          30

Pro His Ala Lys Lys Lys Ser Lys Ile Ser Ala Ser Arg Lys Leu Gln
          35          40          45

Leu Lys Thr Leu Leu Leu Gln Ile Ala Lys Gln Glu Leu Glu Arg Glu
          50          55          60

Ala Glu Glu Arg Arg Gly Glu Lys Gly Arg Ala Leu Ser Thr Arg Cys
65          70          75          80

Gln Pro Leu Glu Leu Ala Gly Leu Gly Phe Ala Glu Leu Gln Asp Leu
          85          90          95

Cys Arg Gln Leu His Ala Arg Val Asp Lys Val Asp Glu Glu Arg Tyr
          100          105          110

Asp Ile Glu Ala Lys Val Thr Lys Asn Ile Thr Glu Ile Ala Asp Leu
          115          120          125

Thr Gln Lys Ile Phe Asp Leu Arg Gly Lys Phe Lys Arg Pro Thr Leu
          130          135          140

Arg Arg Val Arg Ile Ser Ala Asp Ala Met Met Gln Ala Leu Leu Gly
145          150          155          160

Ala Arg Ala Lys Glu Ser Leu Asp Leu Arg Ala His Leu Lys Gln Val
          165          170          175

Lys Lys Glu Asp Thr Glu Lys Glu Asn Arg Glu Val Gly Asp Trp Arg
          180          185          190

Lys Asn Ile Asp Ala Leu Ser Gly Met Glu Gly Arg Lys Lys Lys Phe
          195          200          205

Glu Ser
          210

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1. An in vitro prognosis method for halted bleeding in a patient suffering from postpartum haemorrhage without any invasive procedure, comprising the following steps:

- a) determining, from a biological sample of said patient, the plasmatic fibrinogen concentration, troponin blood concentration and prothrombin time;
- b) examining at least two clinical markers of said patient chosen from the group consisting of heart rate and the presence of placenta anomalies;
- c) calculating a Z score as per the following formula:

$$Z = a + b + c + d + e,$$
 - i) where a is associated with the existence of placenta anomalies in said patient, with a having a value of 0 if no placental anomaly is observed in said patient, and a having a value of 1 if one or more placenta anomalies are observed in said patient;
 - ii) where b is associated with the heart rate of said patient, with b having a value of 0 if the heart rate of said patient is less than or equal to 115 bpm (beats per minute) and b having a value of 1 if the heart rate is higher than 115 bpm;
 - iii) where c is associated with the plasmatic fibrinogen concentration of said patient, with c having a value of

0 if said level is equal to or higher than 2 g/L and c having a value of 1 if said level is lower than 2 g/L;

- iv) where d is associated with the blood troponin concentration of said patient, with d having a value of 0 when said concentration is lower than the detection threshold, and d having a value of 1 if said concentration is higher than or equal to the detection threshold;
- v) where e is associated with the prothrombin time (PT) of said patient, e having a value of 0 if said prothrombin time is higher than or equal to 50%, and e having a value of 1 if said prothrombin time is less than 50%;

wherein a Z score higher than or equal to a value of 2 is indicative of the need to carry out invasive procedure to stop bleeding in said patient suffering from postpartum haemorrhage.

2. The method according to claim 1, characterized in that said biological sample is a blood sample.

3. The method according to claim 1, characterized in that the troponin is troponin I.

4. The method according to claim 3, characterized in that troponin I is cardiac troponin I.

5. The method according to claim 1, characterized in that d has a value of 0 if the blood troponin concentration is lower than 1 pg/L.

6. The method according to claim 1, characterized in that the placentation anomalies are chosen from the group consisting of placenta praevia, placenta accreta, placenta increta, and placenta percreta.

7. The method according to claim 1, characterized in that said invasive procedure is haemostatic surgery or uterine arterial embolisation.

8. The method according to claim 7, characterized in that said invasive procedure is haemostatic surgery chosen from the group comprising hysterectomy, vessel ligation, and intra-abdominal packing.

9. The method according to claim 1, characterized in that it may also include the determination of other biological parameters.

10. The method according to claim 1, characterized in that d has a value of 0 if the blood troponin concentration is lower than 10 pg/L.

* * * * *

专利名称(译)	与产后出血相关的新方法预后		
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其他公开文献	US8784313		
外部链接	Espacenet USPTO		

摘要(译)

本发明涉及一种体外预防方法，用于在没有侵入性操作的情况下阻止患有产后出血的患者的出血，包括以下步骤：(a)使用来自所述患者的生物样品确定血浆纤维蛋白原浓度，血肌钙蛋白浓度以及凝血酶原时间；(b)研究所述患者的至少两种临床标志物，选自心率和胎盘异常的存在；(c)根据以下等式计算得分Z： $Z = a + b + v + d + e$ ；其中a与所述患者中存在胎盘异常相关，当在所述患者中未观察到胎盘异常时为0，并且当在所述患者中观察到一个或多个胎位异常时为0；其中b与所述患者的心率相关，当所述患者的心率为b时，b为0当心率大于115 bpm时，患者小于或等于115 bpm（每分钟心跳次数），b为1；其中c与所述患者的血浆纤维蛋

白原浓度相关，当所述浓度大于或等于2g / L时c为0，当所述浓度小于2g / L时c为1;其中d与所述患者的血液肌钙蛋白浓度相关，当所述浓度小于检测截止值时d为0，当所述浓度大于或等于检测截止值时d为1;其中e与所述患者的凝血酶原时间（PT）相关，当所述凝血酶原时间大于或等于50%时e为0，并且当所述凝血酶原时间小于50%时e为1;其中得分Z大于或等于值2表示需要执行侵入性程序以阻止所述产后患者的出血出血。

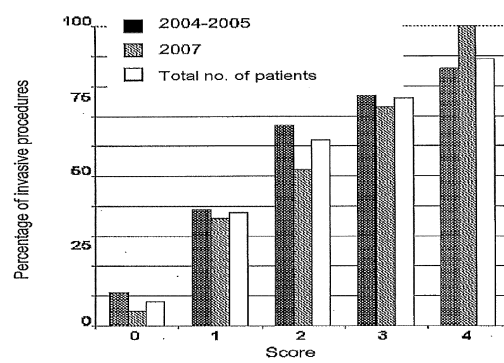


FIGURE 1