Judging Urgency in 343 Ectopic Pregnancies Prior to Surgery – The Importance of Transvaginal Sonographic Diagnosis of Intraabdominal Free Blood

Beurteilung der operativen Dringlichkeit in 343 Eileiterschwangerschaften – die Bedeutung von freiem intraabdominalem Blut in der Transvaginalsonografie

Authors
Janna Pape[1,2], Anahita Bajka[1], Burkhardt Seifert[3], Lars Asmis[4], Patrick Imesch[1], Julian Metzler[1], Tilo Burkhardt[5], George Condous[6], Eleftherios Pierre Samartzis[1,7], Michael Bajka[1]

Affiliations
1 Gynecology, University Hospital Zurich, Zurich, Switzerland
2 Gynecologic Endocrinology and Reproductive Medicine, Inselspital University Hospital Bern, Bern, Switzerland
3 Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland
4 Center for perioperative thrombosis and hemostasis, University of Zurich, Zurich, Switzerland
5 Obstetrics, University Hospital Zurich, Zurich, Switzerland
6 Acute Gynecology, Early Pregnancy & Advanced Endoscopic Surgery Unit, University of Sydney - Sydney Medical School Nepean, Sydney, Australia
7 Gynecology, Research Institute of the McGill University Health Centre, Montreal, Canada

Key words
ultrasound, free fluid, urgency, laparoscopy, ectopic pregnancy

received 15.2.2022
akzeptiert nach Revision 19.10.2022

Bibliography
Ultraschall in Med
DOI 10.1055/a-1967-2134
ISSN 0172-4614

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Dr. Janna Pape
Gynecology
University Hospital Zurich
Rämistrasse 100
8091 Zurich, Switzerland
jannapape91@gmail.com
j_pape03@uni-muenster.de

Additional material is available at https://doi.org/10.1055/a-1967-2134.

ABSTRACT

Objectives Assessing urgency in ectopic pregnancies (ECP) remains controversial since the disorder covers a large clinical spectrum. Severe conditions such as acute abdomen or hemodynamic instability are mostly related to intra-abdominal blood loss diagnosed as free fluid (FF) on transvaginal sonography (TVS). The aims of the current study were to investigate the value of FF and to assess other potentially predictive parameters for judging urgency.

Methods Retrospective cohort analysis on prospectively collected cases of proven ECP (n = 343). Demographics, clinical and laboratory parameters, and findings on TVS and laparoscopy (LSC) were extracted from the digital patient file. FF on TVS and free blood (FB) in LSC were evaluated. Low urgency was defined as FB (LSC) < 100 ml and high urgency as FB (LSC) ≥ 300 ml. The best subset of variables for the prediction of FB was selected and predictors of urgency were evaluated using receiver operator characteristic (ROC) curves.

Results Clinical symptoms, age, β-HCG, hemoglobin (HB) preoperative, and FF were examined in multivariate analysis for the cutoff values of 100 ml and 300 ml. FF was the only independent predictor for low and high urgency; HB preoperative was only significant for high urgency offering marginal improvement. ROC analysis revealed FF as an excellent discriminatory parameter for defining low (AUC 0.837, 95% CI 0.794–0.879) and high urgency (AUC 0.902, 95 % CI 0.860–0.945).

Conclusion Single assessment of FF on TVS is most valuable for judging urgency. However, the exact cutoff values for a low- and high-risk situation must still be defined.

ZUSAMMENFASSUNG

Ziele Die Beurteilung der Dringlichkeit bei ektopen Schwangerschaften ist aufgrund des breiten klinischen Spektrums schwierig. Schwere Verläufe (akutes Abdomen

oder hämodynamische Instabilität) sind meist mit intraabdominalem Blutverlust verbunden, welcher als freie Flüssigkeit (FF) mittels transvaginaler Sonografie (TVS) diagnostiziert werden kann. Ziel der vorliegenden Studie war es, den diagnostischen Wert der FF sowie andere potenziell prädiktive Parameter für die Beurteilung der Dringlichkeit zu untersuchen.

Methode Retrospektive Kohortenanalyse von prospektiv erhobenen Fällen (n=343) mit nachgewiesener ektopen Schwangerschaft. Demografische Daten, Klinik, Laborparameter, sonografische und Befunde der Laparoskopie (LSC) wurden einbezogen. Die Bewertung von FF in der TVS und freiem Blut (FB) in der LSC erfolgte anhand des Bildmaterials. FB < 100ml wurde als wenig- und ≥ 300ml als hochdringlich definiert. Die besten Variablen für die Vorhersage von FB wurden bestimmt und ihre Prädiktion der Dringlichkeit mittels ROC-Kurven bewertet.

Ergebnisse Klinik, Alter, β-HCG, präoperatives Hämoglobin (HB) und FF wurden in einer multivariaten Analyse für die Cut-off-Werte 100ml und 300ml untersucht. Zur Bestimmung geringer (AUC 0,837, 95% CI 0,794–0,879) und hoher Dringlichkeit (AUC 0,902, 95% CI 0,860–0,945) war FF ein hervorragend diskriminierender Parameter; das HB erbrachte nur eine marginale Verbesserung der Vorhersagekraft und nur für hohe Dringlichkeit.

Schlussfolgerungen FF ist für die Beurteilung der Dringlichkeit am wertvollsten, wobei die genauen Grenzwerte für eine Niedrigrisiko- oder Hochrisikosituation festzulegen bleiben.

Introduction

In the last two decades, substantial progress has been made in the diagnosis of ectopic pregnancy (ECP) by transvaginal sonography (TVS), leading to direct ECP visualization in the vast majority of cases [1, 2, 3, 4, 5, 6]. In contrast, urgency remains debatable since the clinical course of ECP covers a large spectrum with different prognoses. It varies from spontaneous resolution as described in 42% of cases [7], including cases without [8] or only limited free fluid (FF) on TVS [9], justifying expectant [7, 10] or conservative [11] management, to a potentially life-threatening condition, indicating emergency intervention without delay [12].

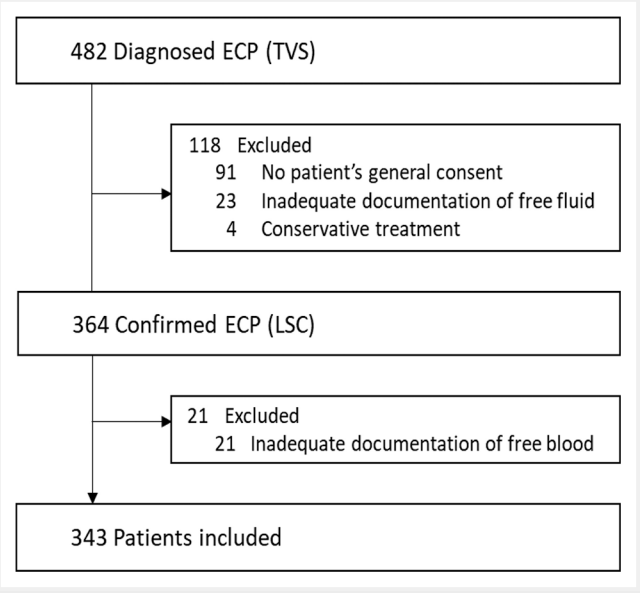
Usually, the danger arising from ECP is defined by severe conditions such as abdominal pain, acute abdomen, low or decreasing venous hemoglobin levels (HB), and hemodynamic instability [13, 14, 15, 16, 17]. All these conditions are mostly related to occult intra-abdominal blood loss diagnosed as FF on TVS and confirmed as free blood (FB) in laparoscopy (LSC), appearing as hemoperitoneum with liquid and clotted parts [6].

Any assessment of FB is more or less imprecise [18] even if based on intraoperative blood aspiration [12]. However, in cases with a suspicion of ECP, the amount of FF on TVS was found to correlate with FB in LSC, paving the way to comprehensively define preoperative urgency. An estimate of FB 300–400 mL has been proposed as a preoperative cutoff value to diagnose severe hemorrhage, declaring high urgency as well as the need for rapid operative intervention [5, 12, 19, 20].

In this study, we investigated the value of FF assessment on TVS and other potentially predictive factors to define not only high but also low urgency.

Methods

This study is a retrospective cohort analysis on prospectively collected cases between January 2012 and March 2020 of laparoscopically investigated ECP. Only cases with adequate documentation of FF on TVS and FB in LSC were included (▶ **Abb. 1**).



▶ **Abb. 1** Flowchart showing the 482 patients with diagnosed ectopic pregnancy (ECP) on transvaginal sonography (TVS), advised to undergo operative confirmation and treatment by laparoscopy (LSC), who were eligible for this study.

We extracted demographics, risk factors, clinical and laboratory findings, TVS examinations, and findings in laparoscopy from the **patient's digital chart file** (▶ **Tab. 1**). All **laboratory** measures including the exact time of each blood examination were assessed (compare ▶ **Tab. 1**): The last HB before operation, the first HB after operation, the difference between them, and the last β-HCG before operation.

The **sonographic examination** was typically performed in a supine position on a gynecologic chair with a slightly elevated upper body. This examination was usually done by a resident on duty and supervised by a staff physician. FF includes different types of blood consistency with liquid and clotted parts. In case of ECP, we counted any representation of FF found in the pelvic or abdominal cavity as part of FB, independently from its echogenicity [6,

▶**Tab. 2** Liquids and clots. Liquid and clotted free fluid (FF) on transvaginal sonography (TVS) and liquid and clotted free blood (FB) in laparoscopy (LSC) were correlated using Spearman's rank correlation. Free fluid "not defined" was excluded from the calculation.

		Liquid free blood (LSC)					
		No	**Mild**	**Moderate**	**Severe**	**Total**	**P**
Liquid free fluid (TVS)		**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
	No	45 (50)	40 (34)	5 (9)	6 (8)	96 29)	<0.001
	Mild	26 (29)	61 (52)	31 (54)	10 (14)	128 (38)	
	Moderate	8 (9)	10 (9)	12 (21)	13 (18)	43 (13)	
	Severe	11 (12)	6 (5)	9 (16)	43 (60)	69 (21)	
	Total	90 (100)	117 (100)	57 (100)	72 (100)	336 (100)	
		Clotted free blood (LSC)					
		No	**Mild**	**Moderate**	**Severe**	**Total**	**P**
Clotted free fluid (TVS)		**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
	No	98 (63)	26 (44)	12 (26)	4 (6)	140 (42)	<0.001
	Mild	41 (26)	23 (39)	14 (30)	9 (13)	87 (27)	
	Moderate	16 (10)	9 (15)	17 (36)	16 (23)	58 (18)	
	Severe	1 (1)	1 (2)	4(9)	41 (59)	46 (14)	
	Total	159 (100)	59 (100)	44 (100)	70 (100)	331 (100)	

Data are given as n (%). **Definitions of semiquantitative groups of liquid and clotted FF (TVS)**: no FF, mild FF (only in the pouch of Douglas (POD), less than 3×3 cm); moderate FF (only in the POD, more than 3×3 cm, but not exceeding uterine fundus); severe FF (in POD, exceeding the uterine fundus). **Definitions of quantitative groups for liquid and clotted FB (LSC)**: no FB (0 ml); mild FB (1–99 ml), moderate FB (100–299 ml), severe FB (≥ 300 ml) based on inspection and estimation, not necessarily by aspiration and quantification.

19, 20, 21, 22]. Following the concept of the sentinel clot, which appears first in the vicinity of the bleeding source [23, 24], we primarily relied on TVS (▶ **Abb. 2**), and, if needed, extended the examination by transabdominal sonography (TAS) to assess the entire abdomen, especially Morison's pouch (hepatorenal, right upper abdomen) and Koller's pouch (lienorenal, left upper abdomen).

FF (TVS) was not described in detail in the clinical routine, so that three experienced sonographers reviewed the complete dataset. The experts rated each case regarding the total amount of FF in milliliters, as well as separately for liquids and clots, and assigned them to one of the four semiquantitative categories (▶ **Tab. 2**): no FF, minimal FF (only in pouch of Douglas (POD), less than 3 × 3 cm), moderate FF (only in the POD more than 3 × 3 cm), severe FF (in the POD more than 3 × 3 cm and/or adnex and/or excavatio vesicouterina and/or Morison's pouch), trapped fluid outside the ovary (e.g., hematosalpinx) or inside the ovary (e.g., corpus luteum graviditatis) was not counted as FF [6]. In cases of divergent estimates, the reviewers tried to achieve consent through discussion. Otherwise, the opinion of the majority (2 to 1) was recorded.

The beginning of LSC was assessed by its protocolled start time. We defined the complete **intraperitoneal FB** as being equal to hemoperitoneum, and equal to the total amount of FB, clotted, and liquid together (▶ **Abb. 2**). FB was estimated by the operator regularly at the beginning of the operation, not necessarily being measured by aspiration. Only in cases of low or very low quantities, where numeric estimations were not given, we transformed the verbal descriptions as follows: "no" to 0 mL, "minimal" to 10 mL, "few" to 30 mL, "some" to 50 mL, thereby consciously assigning these descriptions to the group of FB < 100 mL. Similar to FF, we divided FB into four categories (▶ **Tab. 2**) and assessed it separately for liquid and clots. We set the stop of bleeding equal to the beginning of the operation. Furthermore, the presence or absence of ECP rupture was recorded.

We investigated the value of FF assessment on TVS as well as other potentially predictive factors for defining not only **high (FB ≥ 300 mL)** but also **low urgency (FB < 100 mL)** (▶ **Abb. 2**, image 2a).

Data were collected in Microsoft Excel (Excel 2019, Microsoft Corporation, Redmond, Washington, USA). Statistical analyses were performed using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as median with interquartile range (IQR) or mean ± standard deviation (SD) with range. Continuous and ordinal variables were correlated using Spearman's rank correlation rho. Changes in continuous and ordinal variables from TVS to LSC were analyzed using Wilcoxon's signed rank test with continuity correction. Differences between groups were assessed using the Wilcoxon rank sum test with continuity correction and the Kruskal-Wallis test. Categorical and ordinal variables are presented as frequencies and percentages. Differences in categorical variables between groups

▶**Tab. 1** Characteristics of study cohort.

Characteristics		Value
Patients, n		343
Anamnesis		
	Age, y (mean ± SD (range))	33.4 ± 5.6 (20.4–46.3)
	Duration of pregnancy after LMP, w + d (mean ± SD (range))	6+3 ± 1+3 (2+0–10+4)
	No birth (0-para), n (%)	204 (59)
	Only vaginal birth (one or more), n (%)	72 (21)
	Only c-section (one or more), n (%)	60 (17)
	Vaginal birth and c-section (one or more each), n (%)	6 (2)
	No notification, n (%)	1
Risk factors (multiple choice possible), n (%)		
	None	141 (41)
	Previous ECP	61 (18)
	Abdominal operations (excluding c-section)	48 (14)
	Infertility treatment	44 (13)
	Smoking	48 (14)
	Infections	22 (6)
	Endometriosis	26 (8)
	ART (current pregnancy)	21 (6)
	IUD in situ	10 (3)
	After sterilization	7 (2)
	Tubal pathology	3 (1)
Clinical symptoms, n (%)		
	None	41 (12)
	Only vaginal bleeding	54 (16)
	Only pain	93 (27)
	Pain and vaginal bleeding, hemodynamically stable	146 (43)
	Hemodynamically unstable	9 (3)
Laboratory findings		
	β-HCG (IU/L) pre-operation (n = 340), median (IQR)*	1978 (657–4638)
	<1500 (IU/L), n (%)	144 (42)
	<100 (IU/L), n (%)	13 (4)
	<20 (IU/L), n (%)	6 (2)
	<1 (IU/L), n (%)	2 (1)
	Hb preoperative (g/L) (n=338), mean ± SD (range)*	125.9 ± 13.7 (39–154)
	Hb postoperative (g/L) (n=189), mean ± SD (range)	102.9 ± 20.1 (41–140)
	Hb difference (g/L) (n=188), mean ± SD (range)	–19.4 ± 14.4 (–59–33)
Treatment		
	Laparoscopy, n (%)**	343 (100)
	Number of preoperative consultations, n (mean ± SD (range)) (n = 342)	2.2 ± 1.0 (1–6)
	Duration of in-house stay, d (mean ± SD (range)) (n = 329)	1.9 ± 1.1 (1–8)

Data are given as n (%), mean ± SD, median (IQR). * Only the last measurement before the operation was considered. ** Including two conversions to laparotomy. ART: artificial reproduction therapy; CUA: congenital uterine anomaly; ECP: ectopic pregnancy; FB: free blood; FF: free fluid; HB: venous hemoglobin concentration; β-HCG: β-human chorionic gonadotropin; IUD: intrauterine contraceptive device; LSC: laparoscopy.

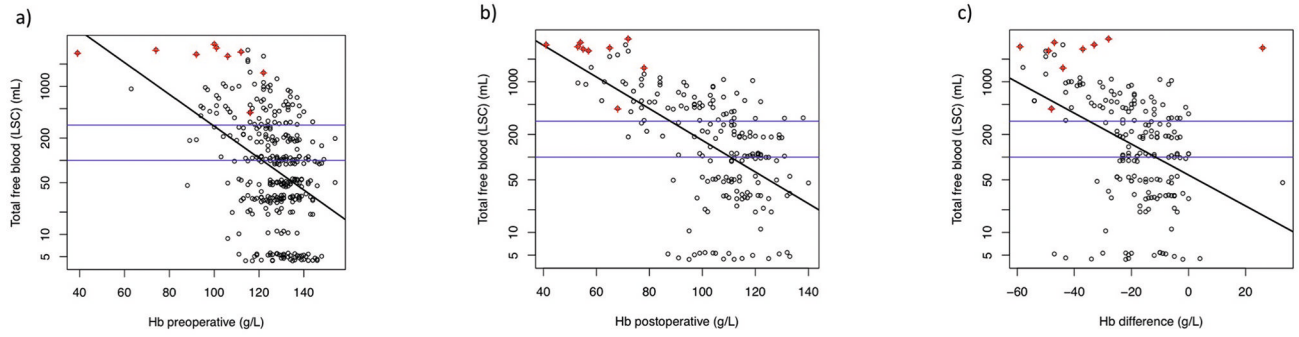
were assessed using Pearson's chi-square test and Fisher's exact test as appropriate. Proportions like sensitivity, specificity, positive and negative predictive value are presented with 95% Wilson confidence intervals (CI). Two-sided p-values less or equal to 0.05 were considered statistically significant. Univariate and multivariable linear regressions were performed to predict FB. Variables with skew distributions were logarithmically transformed for these analyses. For transformations, zero values of FF and FB were set to 10 mL. Variables were included based on p-values < 0.2 in univariate analyses and clinical knowledge. A best subset of variables for prediction of FB was selected based on the Bayesian information criterion (BIC) using the procedure bestglm. The best model was used in logistic regressions to predict low and high urgency. The results are presented as odds ratios (OR) with 95% CI. Predictors of urgency were evaluated using receiver operator characteristic (ROC) curves and presented as areas under the curve (AUC) with 95% CI.

Prior to this retrospective study, ethics approval by the local ethics committee was obtained. Only patients who provided written general consent for the incorporation of their data into research were included. This study considered the STROBE criteria.

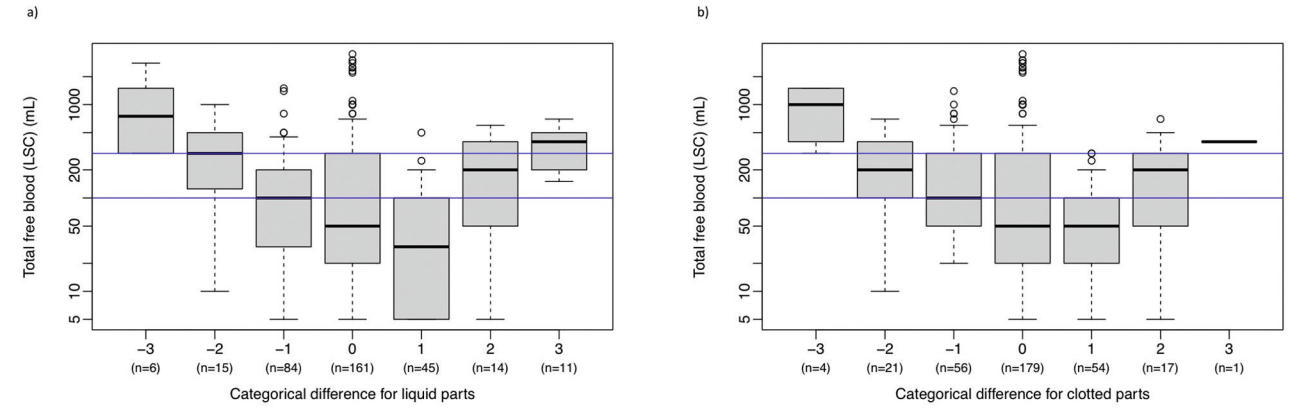
Results

In total, 343 patients with confirmed tubal and nontubal ECP and adequately documented FF on TVS and FB in LSC were included (▶ **Abb. 1**). Demographics are given by ▶ **Tab. 1**. Based on the literature and our own experience, we analyzed a selection of potentially predictive factors to define urgency in ECP (**Supplementary Table 1**).

Time of diagnosis and clinical presentation. In our cohort, the great majority (85%, 293/343) declared symptoms such as pain and/or vaginal bleeding. No asymptomatic patient (with LMP) presented severe FB ≥ 300 mL before 7+0 (weeks + days)



▶ **Abb. 4** Hemoglobin concentration (HB) and total intra-abdominal free blood (FB) in laparoscopy (LSC). Relation between **a** HB before the operation, **b** HB after the operation, **c** HB difference between them, and the confirmed amount of FB in LSC (equal to hemoperitoneum). Values of FB are jittered, making overlapping data points visible. Blue lines mark FB at 100 ml and 300 ml. Red plus signs indicate cases with circulatory instability. Black line represents linear regression of FB in all cases. Only in one case of hemodynamic instability (FB was 2500 ml), postoperative HB was measured after the administration of two RBC, resulting in an HB difference of +26 g/L. Only one patient with FB 50 ml showed a higher Hb difference of +33 g/L which remained unexplained.



▶ **Abb. 5** Liquids and clots. Deviations of liquid and clotted free fluid (FF) on transvaginal sonography (TVS) from liquid **a** and clotted **b** free blood (FB) in laparoscopy (LSC) are presented as subtraction of the assigned category number (no FF = 1, mild FF = 2, moderate FF = 3, severe FF = 4, for details compare Table 2). Negative values (to the left) indicate underestimation, positive values (to the right) indicate overestimation of liquid **a** or clotted parts **b** of FB. The blue lines mark FB at 100 ml and 300 ml.

(▶ **Tab. 1**). Only one asymptomatic woman (2%, 1/41) had sonographically diagnosed FF and operatively confirmed FB of 300 mL, but at 7+5 with β-HCG 1,103 IU/L. She had no prior history of ECP and received infertility treatment. Furthermore, all nine patients with hemodynamic instability (3%, 9/343) presented severe FB (▶ **Abb. 3**). Here, pregnancy was diagnosed in consequence of the emergency examination, and not before, taking place in two patients at 4+0 or earlier, and in three patients at 7+0 or later.

Hemoglobin: Pre- and postoperative HB as well as its difference correlated significantly with FB (LSC) (all $p < 0.001$) (▶ **Abb. 4**, **Supplementary Table 1**).

Hemoglobin: Pre- and postoperative HB as well as its difference correlated significantly with FB (LSC) (all $p < 0.001$) (**Supplementary Table 1**).

Hemodynamic instability. Seven of the patients with hemodynamic instability (78%, 7/9) were diagnosed with FF 1,657 ± 883 (400–3,000) and confirmed as hemoperitoneum of FB 2,478 ± 924 (500–3,500) (mL, mean ± SD (range)). Conversion to laparotomy was necessary in two cases. The preoperative HB (96 ± 26 (39–122)), postoperative HB (60 ± 12 (41–78)), and HB difference (43 ± 10 (28–59) (g/L) correlated significantly with FB. The operators defined hemoperitoneum as a consequence of slow but long-lasting bleeding (89%, 8/9) rather than as a result of a sudden rise in bleeding due to arrosion of one or more bigger vessels (11%, 1/9) (▶ **Abb. 2**).

Correlation of FF (TVS) with FB (LSC). We found a strong correlation between the total amounts of FF and FB (Spearman's rank correlation $p < 0.001$, rho = 0.7) (**Supplementary Table 1**, ▶ **Abb. 3**).

Liquid and clotted parts. We found moderate to high correlations between FF on TVS and FB in LSC, for both liquid (rho 0.47, $p < 0.001$) and clotted parts (rho 0.60, $p < 0.001$) (▶ **Abb. 3**). No difference was found between the categories of liquid and clotted parts, comparing FF and FB (▶ **Tab. 2**). Otherwise, the difference between these parts depended significantly on the amount of FB ($p < 0.001$, Kruskal-Wallis rank sum test): In higher total amounts of FF, deviations were greater, both in terms of under- and overestimation (▶ **Abb. 5**). However, there was no evidence of a systematic error to under- or overestimate liquids or clots (p 0.15 and 0.30, Wilcoxon signed rank test with continuity correction).

▶**Tab. 3** Multivariate analysis of elaborated independent predictors of intra-abdominal free blood in laparoscopy (LSC), focused on < 100 ml and ≥ 300 ml. All subsets of the five variables (clinical symptoms, age, β-HCG, HB preoperative, FF) were compared (2^5 = 32 models).

		Free blood (LSC)				
		MLR*	BIC OLRM**, LR***			
			< 100 ml		≥300 ml	
Parameter		**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Clinical symptoms		<0.001				
	None	reference				
	Only vaginal bleeding (n)	0.2				
	Only pain (n)	0.006				
	Pain and vaginal bleeding (n), hemodynamically stable	0.023				
	Hemodynamically unstable (n)	0.001				
Age (years)		0.55				
β-HCG preoperative (IU/L) Δ		0.79				
HB preoperative (g/L)		0.024	1.015 (0.991–1.041)	0.24	0.966 (0.939–0.993)	0.015
FF total (ml) Δ		<0.001	0.102 (0.060–0.168)	<0.001	30.1 (13.0–81.1)	<0.001

*MLR: multivariable linear regression. **BIC OLRM: Bayesian information criterion optimal linear regression model.***LR: logistic regression. Δlog10 transformed. "Clinical symptoms: none" served as the reference for the other clinical symptoms.

Major bleeding site. Tubal ECP, representing 91% (311/343) of all confirmed ECP, showed FB of 100 mL (median, range 0–3,000 mL). The other seven ECP locations together covered 9%, showing very differing amounts of FB (▶ **Abb. 6**). Due to the low numbers in all locations other than tubal ECP, major bleeding site was not used for risk stratification.

Risk stratification of intraperitoneal hemorrhage. The following factors correlated significantly with the total amount of FB in LSC (**Supplementary Table 1**): the absence of clinical symptoms, only vaginal bleeding, only pain, hemodynamic instability, age, HB pre- and postoperative, HB difference, FF, also in its morphologically different aspects (FF liquid and clotted), and ruptured ECP. In **univariate analysis** (**Supplementary Table 1**), most of these factors correlated significantly with the total amount of FB (LSC), examined also for two different cutoff values (100 mL and 300 mL). We did not process the clearly not significant parameters (obstetric history), underpowered (hemodynamically unstable), postoperative (HB postoperative, HB difference, ruptured ECP) as well as factual dependent parameters (FF clotted and FF liquid). In **multivariable linear regression** (▶ **Tab. 3**), we analyzed clinical symptoms as a categorical variable with five categories of symptoms. In this analysis, clinical symptoms, HB preoperative, and FF were significant predictors of FB. Best subset selection among 32 tested models found FF together with preoperative HB as the BIC optimal predictor. The second-best model consisted of FF alone. In the **logistic regressions** for prediction of low and high urgency, FF was the only independent predictor for both low and high urgency. Preoperative HB was only significant for high urgency (▶ **Tab. 3**).

ROC analysis revealed FF (TVS) as an excellent discriminatory parameter for defining low urgency as well as high urgency. Adding preoperative HB to FF revealed only a marginal, probably clinically not relevant improvement in the prediction of FB in LSC for defining high urgency (▶ **Abb. 7**). The Youden Index based on the calculated ROC curves was used to determine the best differentiating threshold for low and high urgency. The optimum cutoff value for predicting low urgency (FB < 100 mL) was 150 mL FF; the optimum cutoff value for predicting high urgency (FB ≥ 300 mL) was 250 mL FF (▶ **Tab. 4**).

Outcome and survival: All 343 patients recovered from ECP and left the hospital within 8 days.

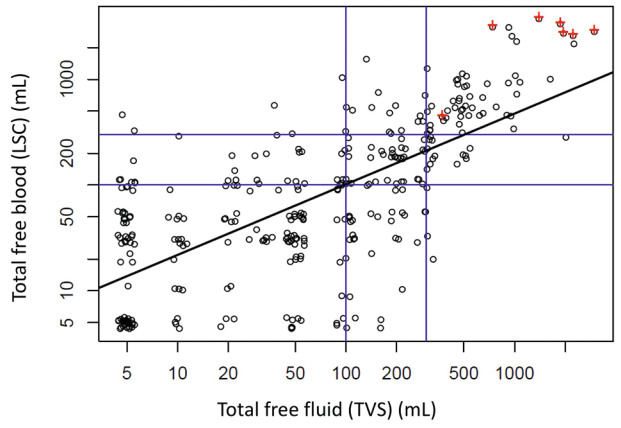
Discussion

Our study revealed FF on TVS as the main factor for reasonably defining low and high urgency in ECP.

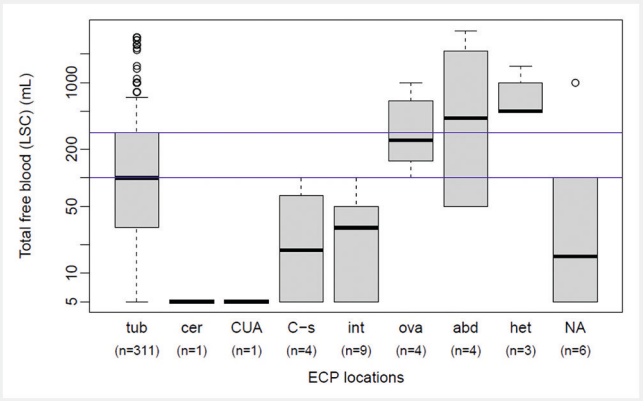
Time of diagnosis and clinical presentation. None of the asymptomatic patients with LMP (12%, 41/343) presented severe FB (LSC) before 7+0 (weeks + days). Furthermore, none of the patients with hemodynamic instability (3%, 9/343) were aware of their pregnancy, since no one had attended regular first pregnancy examination before 7+1 or had done a urine pregnancy test as usual when menstruation is lacking.

The correlation of FF (TVS) with FB (LSC) was highly significant, not only for the total amounts (▶ **Abb. 3**) but also for liquid and clotted parts separately (▶ **Abb. 5**, ▶ **Tab. 2**). The time-related differences between the assessments in TVS and LSC are considered to be irrelevant. TVS is well known as a reliable method

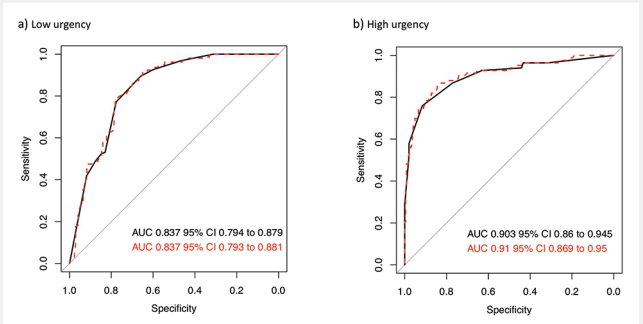
▶ **Abb. 2** Appearance of severe hemoperitoneum on transvaginal sonography (TVS) and laparoscopy (LSC), defined as ≥ 300 ml intra-abdominal free blood (FB). **1a** TVS diagnosis: severe liquid and mild clotted free fluid (FF), 700 ml, **1b** LSC confirmation: moderate liquid and severe clotted FB, total 600 ml. **2a** TVS: severe liquid and mild clotted FF, 1500 ml, **2b** LSC: severe liquid and moderate clotted FB, 1000 ml. **3a** TVS: moderate liquid and severe clotted FF, 1500 ml, **3b** LSC: severe liquid and severe clotted FB, 3000 ml, spurting arterial bleeding. **4a** TVS: severe clotted FF, 700 ml, **4b** LSC: severe clotted and moderate liquid FB, 1000 ml.



▶ **Abb. 3** Total amounts of diagnosed free fluid on transvaginal sonography (TVS) in relation to confirmed free blood in laparoscopy (LSC). Values of free blood are jittered, making overlapping data points visible. Blue lines mark free fluid and free blood at 100 ml and 300 ml. Black line represents linear regression. Free fluid was only recorded in 7 of 9 hemodynamically instable patients (red plus signs).



▶ **Abb. 6** Ectopic pregnancy (ECP) location and intra-abdominal free blood. Arrangement of groups according to the median of free blood in comparison to tubal ECP, the strongest group representing 91% (311/343) of cases. The blue lines mark free blood at 100 ml and 300 ml. Abd: abdominal; cer: cervical; CUA: in congenital uterine anomaly; C-s: in C-section scar; het: heterotopic; NA: location not available; int: interstitial; ova: ovarian; tub: tubal.



▶ **Abb. 7** ROC analysis for the prediction of the total amount of intra-abdominal free blood (FB) in laparoscopy (LSC) presenting the favorite parameters resulting from multivariate analysis, separate for **a** low urgency (FB < 100 ml), and **b** high urgency (FB ≥ 300 ml). Predictors of urgency were presented as area under the curve (AUC) with 95% confidence intervals. The black solid line represents free fluid (FF) on TVS alone. The red dotted line represents the combination of FF (TVS) and preoperative hemoglobin.

for assessing FF in the pelvis [5, 6, 12, 21, 25, 26, 27] whereas different semiquantitative approaches have been applied [6, 9, 12, 19, 21]. We found the equivalent of a hemoperitoneum of 300 mL in a POD filled with FF of any echogenicity, and just exceeding the edge of the fundus on TVS (▶ **Abb. 2**, image 2a). It is an easily reproducible landmark and in perfect agreement with other assessments [5, 9, 12].

Liquid and clotted parts. A blurred uterus contour or a generally remarkably reduced view may serve as strong indicators for clots in contact with the uterus (▶ **Tab. 2**). For liquid and clotted parts, a higher amount of FB correlated with higher deviations of TVS-estimated FF (▶ **Abb. 5**). Although the occurrence of clots may be considered an indicator for urgency [12], we found that liquid and clotted parts on TVS and LSC typically appeared in an approximately 1:1 relation between 100 mL and 1000 mL, so that differentiation of liquidity would probably not help to define urgency (▶ **Abb. 5**).

▶**Tab. 4** Testing different cutoff values of free fluid (FF) on transvaginal sonography (TVS) to predict intra-abdominal free blood (FB) in laparoscopy (LSC), separately for low urgency (defined as FB < 100 ml) and high urgency (defined as FB ≥ 300 ml).

	Low urgency			
	Sens.	**Spec.**	**PPV**	**NPV**
Free fluid (TVS)	**(%)**	**(%)**	**(%)**	**(%)**
(ml)	**(95% CI)**	**(95% CI)**	**(95% CI)**	**(95% CI)**
<10	30.9	92.9	80.6	58.5
	24.3–38.4	88.1–95.9	69.1–88.6	52.6–64.2
<50	53.1	82.9	74.8	65
	(45.4–60.6)	(76.6–87.9)	(66.1–81.8)	(58.4–71.0)
<100	77.2	77.6	76.7	78.1
	(70.1–83)	(70.8–83.3)	(69.6–82.5)	(71.3–83.7)
<150	89.5	65.9	71.4	86.8
	(83.8–93.3)	(58.5–72.6)	(64.9–77.2)	(79.9–91.6)
<200	92.6	60	68.8	89.5
	(87.5–95.7)	(52.5–67.1)	(62.4–74.6)	(82.5–93.9)
<300	96.9	46.5	63.3	94
	(93.0–98.7)	(39.1–54)	(57.1–69.1)	(86.8–97.4)
<500	100	28.2	57	100
	(97.7–100)	(22.0–35.4)	(51.2–62.7)	(92.6–100)
<1000	100	10.6	51.6	100
	(97.7–100)	(6.8–16.1)	(46.1–57.1)	(82.4–100)
	High urgency			
	Sens.	**Spec.**	**PPV**	**NPV**
Free fluid (TVS)	**(%)**	**(%)**	**(%)**	**(%)**
(ml)	**(95% CI)**	**(95% CI)**	**(95% CI)**	**(95% CI)**
≥50	94	44.2	35.9	95.7
	(86.7–97.4)	(38.1–50.4)	(29.9–42.5)	(90.2–98.1)
≥100	92.8	63.1	45.6	96.3
	(85.1–96.6)	(56.9–68.8)	(38.2–53.1)	(92.2–98.3)
≥200	83.1	81.9	60.5	93.6
	(73.7–89.7)	(76.7–86.2)	(51.4–69.0)	(89.5–96.1)
≥300	75.9	91.6	75	91.9
	(65.7–83.8)	(87.5–94.4)	(64.8–83.0)	(87.9–94.7)
≥500	51.8	98	89.6	85.9
	(41.2–62.2)	(95.4–99.1)	(77.8–95.5)	(81.4–89.5)
≥1000	21.7	100	100	79.3
	(14.2–31.7)	(98.5–100)	(82.4–100)	(74.5–83.4)

Sens.: sensitivity; spec.: specificity; PPV: positive predictive value; NPV: negative predictive value.

Predictors of intraperitoneal hemorrhage. None of the investigated preoperative parameters was able to predict low or high urgency, except for the assessment of FF on TVS (▶ **Abb. 3**, **Supplementary Table 1**), and notably HB (▶ **Tab. 3**), but only as a low degree additive for the assessment in high urgency (▶ **Abb. 7**). Hemodynamic instability constitutes a common presentation in medically less developed countries. However, in our cohort, these rare events did not have a relevant influence on risk stratification. Moreover, stable hemoperitoneum with ECP undergoing spontaneous resolution may be treated expectantly. Pain was a significant indicator for "not low urgency" only in univariate analysis. The optimum cutoff value was FF = 150 mL for predicting low urgency, and FF = 250 mL for high urgency (▶ **Abb. 7**). The search for reasonable cutoff values may also be based on > 90% sensitivity for defining high urgency and > 90% specificity for defining low urgency (▶ **Tab. 4**). This approach would lead to FF < 10 mL determining low urgency and FF ≥ 100 mL determining high urgency, which is substantially more restrictive than the cutoffs we had empirically chosen. Prospective clinical studies should determine the meaningful application of cutoff values for FF assessment in diagnosing FB.

Possible limitations of the study are its retrospective design, the impracticality of precise free fluid assessment even during laparoscopy, and the lack of reproducibility. Gestational age is based only on the reported LMP so that we cannot exclude a stronger influence of this parameter on urgency. In our cohort, 44 women became pregnant following fertility treatment, whereby the potential confounder of an increased amount of FF after ovarian stimulation cannot be excluded. Strengths included the high denominator, the histological ECP diagnosis, and the gold standard outcomes. Future considerations should include the implementation of this approach in a multicenter study.

We conclude that assessing FF on TVS is of outmost relevance in assigning low and high urgency, supporting an optimum ECP management. The more FF in TVS, the higher the urgency. However, the exact cutoff values remain debatable. We found the equivalent of a hemoperitoneum of 300 mL, defining high urgency, in a POD filled with FF of any echogenicity, and just exceeding the edge of the fundus on TVS.

Fundings

EMDO | EMDO Stiftung | http://dx.doi.org/10.13039/501100008464

Acknowledgement

Our deep thanks go to the patients and all members of our Department of OB/GYN and Reproductive Endocrinology at the University Hospital of Zurich for their dedication and great support in this project, especially to Mrs. Carla Trachsel, and Dr. Deivis Strutas. This project was supported by a generous research grant of the EMDO Foundation, Zurich, Switzerland.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Condous G, Okaro E, Khalid A et al. The accuracy of transvaginal ultrasonography for the diagnosis of ectopic pregnancy prior to surgery. Hum Reprod 2005; 20–1409

[2] Jurkovic D, Mavrelos D. Catch me if you scan: ultrasound diagnosis of ectopic pregnancy. Ultrasound Obstet Gynecol 2007; 30–7

[3] Casikar I, Reid S, Condous G. Ectopic pregnancy: Ultrasound diagnosis in modern management. Clin Obstet Gynecol 2012; 55–409

[4] Kirk E, Bottomley C, Bourne T. Diagnosing ectopic pregnancy and current concepts in the management of pregnancy of unknown location. Hum Reprod Update 2014; 20–261

[5] Dooley WM, Chaggar P, De Braud LV et al. Effect of morphological type of extrauterine ectopic pregnancy on accuracy of preoperative ultrasound diagnosis. Ultrasound Obstet Gynecol 2019; 54–544

[6] Pape J, Bajka A, Strutas D et al. The predictive value of decisive and soft ultrasound criteria for ectopic pregnancy identification in 321 preoperative cases. Ultraschall in Med 2021

[7] Elson J, Tailor A, Banerjee S et al. Expectant management of tubal ectopic pregnancy: prediction of successful outcome using decision tree analysis. Ultrasound Obstet Gynecol 2004; 23–556

[8] Mol BW, Hajenius PJ, Engelsbel S et al. Can noninvasive diagnostic tools predict tubal rupture or active bleeding in patients with tubal pregnancy? Fertil Steril 1999; 71–173

[9] Bignardi T, Condous G. Does tubal ectopic pregnancy with hemoperitoneum always require surgery? Ultrasound Obstet Gynecol 2009; 33–715

[10] Mavrelos D, Nicks H, Jamil A et al. Efficacy and safety of a clinical protocol for expectant management of selected women diagnosed with a tubal ectopic pregnancy. Ultrasound Obstet Gynecol 2013; 42–107

[11] Lipscomb GH, McCord ML, Stovall TG et al. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. N Engl J Med 1999; 341–1978

[12] Rajah K, Goodhart V, Zamora KP et al. How to measure size of tubal ectopic pregnancy on ultrasound. Ultrasound Obstet Gynecol 2018; 52–109

[13] AAFP. 2020 . Accessed February.15.2021 at https://www.aafp.org/afp/2020/0515/p599.html

[14] ACOG. Practice Bulletin 191: Tubal ectopic pregnancy. 2018 . Accessed February.15.2021 at https://journals.lww.com/greenjournal/Fulltext/2018/02000/ACOG_Practice_Bulletin_No__191__Tubal_Ectopic.38.aspx

[15] NICE . Accessed February.15.2021 at https://www.nice.org.uk/guidance/ng126/chapter/recommendations

[16] RCOG . Accessed February.15.2021 at https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg21/

[17] UpToDate. Accessed February.15.2021 at https://www.uptodate.com/contents/ectopic-pregnancy-clinical-manifestations-and-diagnosis

[18] Yefet E, Yossef A, Suleiman A et al. Hemoglobin drop following postpartum hemorrhage. Sci Rep 2020; 10(01)

[19] Fauconnier A, Mabrouk A, Salomon LJ et al. Ultrasound assessment of haemoperitoneum in ectopic pregnancy: derivation of a prediction model. World J Emerg Surg 2007; 2

[20] Popowski T, Huchon C, Toret-Labeeuw F et al. Hemoperitoneum assessment in ectopic pregnancy. Int J Obstet Gyn 2012; 116–100

[21] Frates MC, Brown DL, Doubilet PM et al. Tubal rupture in patients with ectopic pregnancy: diagnosis with transvaginal US. Radiology 1994; 191–772

[22] Frates MC, Doubilet PM, Peters HE et al. Adnexal sonographic findings in ectopic pregnancy and their correlation with tubal rupture and human chorionic gonadotropin levels. J Ultrasound Med 2014; 33–703

[23] Baqué P, Iannelli A, Dausse F et al. A new method to approach exact hemoperitoneum volume in a splenic trauma model using ultrasonography. Surg Radiol Anat 2005; 27–253

[24] Lubner M, Menias C, Rucker C et al. Blood in the belly: CT findings of hemoperitoneum. Radiographics 2007; 27(01)–125

[25] Sickler GK, Chen PC, Dubinsky TJ et al. Free echogenic pelvic fluid: correlation with hemoperitoneum. J Ultrasound Med 1998; 17–435

[26] Abrams BJ, Sukumvanich P, Seibel R et al. Ultrasound for the detection of Intraperitoneal Fluid : The role of Trendelenburg positioning. AM J Emerg Med 1999; 17–120

[27] Salomon LJ, Nassar M, Bernard JP et al. A score-based method to improve the quality of emergency gynaecological ultrasound examination. Eur J Obstet Gynecol Reprod Biol 2009; 143–120