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ISTH SSC COMMUNICATIONS

Disseminated intravascular coagulopathy in pregnancy: lessons from an international registry of the International Society for Thrombosis and Hemostasis: communication from the SSC of the ISTH

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Abstract

Disseminated intravascular coagulopathy (DIC) in pregnancy is a severe maternal morbidity that is associated with short- and long-term complications. However, information regarding the causes of DIC treatments and outcomes in pregnancy is based on local reports. To address this gap, 2 Scientific and Standardization Committees, the Women's Health Issues in Thrombosis and Hemostasis and Disseminated Intravascular Coagulation of the International Society on Thrombosis and Hemostasis, joined to establish an international global registry. This registry was developed to examine the current definitions, clinical presentations, and current practices around laboratory diagnosis and management of DIC worldwide. We collected data between

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2018 and 2024; there were 148 data entries to the registry (13 countries); 104 of them included patients' clinical and laboratory information. Placental abruption is the leading cause for ante- and intrapartum DIC, especially when associated with stillbirth. The leading etiology for postpartum DIC was uterine atony, especially following/during caesarean sections. The contribution of abnormally implanted placenta (ie, placenta accreta and/or previa) to the development of DIC is increasing. The leading pregnancy complications associated with DIC were placental abruption in HIC and preeclampsia in LMIC. Hemostatic parameters differed between women who had a positive pregnancy–specific DIC score and those who did not meet that criterion. Women with placental-mediated pregnancy complications had a lower median pregnancy–specific DIC score than those without such complications at the time of diagnosis of DIC and following recovery, suggesting a different mechanism of disease in the 2 groups.

KEYWORDS
blood transfusion, hysterectomy, placenta accreta, postpartum hemorrhage, pregnancy-specific DIC score

1 | INTRODUCTION

Obstetric hemorrhage is a leading cause of maternal mortality [1,2]. Normal pregnancy is associated with a physiologic prothrombotic state resulting in increased thrombin generation [3–7], as an adaptive physiological mechanism, to prevent bleeding. Nevertheless, uncontrolled peripartum hemorrhage is one of the leading causes for maternal mortality worldwide [8–10].

Antepartum and postpartum hemorrhage (PPH) can be associated with disseminated intravascular coagulation (DIC), often secondary to underlying maternal and/or fetal complications [11]. DIC is generally more common in men than women, apart from the reproductive years when pregnancy and its complications increase its prevalence among women [12–14]. DIC rate during pregnancy varies from 0.03% [15] to 0.35% [16]. The most frequent pregnancy complication associated with DIC is placental abruption [17–20] (especially when accompanied by fetal death), followed by PPH and preeclampsia [15,16,21]. PPH accounts for 27% of maternal deaths in the developing regions and 16% of maternal deaths in the developed regions [22]. Identification of women at risk, along with early coordinated intervention, has been shown to decrease maternal morbidity and mortality [23].

The diagnosis of DIC in pregnancy is challenging due to its relatively fast onset and the hypercoagulable state of pregnant women that is manifested in high fibrinogen concentrations and a shorter prothrombin time (PT) value than nonpregnant patients. As a result, DIC is often diagnosed very late, only when the patient suffers from uncontrollable bleeding or multiorgan failure. Diagnostic scores and treatment modalities were developed and may assist the clinician in the diagnosis and management of DIC. Information regarding the causes, treatments, and outcomes of DIC in pregnancy is based on local reports and lacks a global perspective. To address this gap, 2 Scientific and Standardization Committees, including the Women's Health Issues in Thrombosis and Hemostasis and Disseminated Intravascular Coagulation of the International Society on Thrombosis and Hemostasis (ISTH), joined to establish an international global registry on DIC in pregnancy. The registry aims to examine the current definitions, clinical presentations, current practices, laboratory diagnosis, blood product transfusion, and management of DIC worldwide.

2 | METHODS

This is an observational study of an international registry of 2 Scientific and Standardization Committees, including the Women's Health Issues in Thrombosis and Hemostasis and Disseminated Intravascular Coagulation of the ISTH, for the study of the characteristics of DIC in pregnancy. We collected data between 2018 and 2024; there were 148 data entries to the registry (13 countries), and 104 of them included patients' information. The study was approved by the local institutional review boards of the participating centers.

During data entry, DIC was defined according to the discretion of the attending clinicians at the participating centers. ICD-9 code 776.2 was used for the identification of patients with DIC during pregnancy in maternity databases. During the analysis of the data, the pregnancy-specific DIC score was used for comparisons [16].

The DIC questionnaire was available online through the ISTH website (https://redcap.isth.org/surveys/?s=KFC8RN8XWC) for centers that consent to contribute their data. There were 2 questionnaires: (1) global registry of DIC in pregnancy that included the epidemiological data of the participating physician and maternity center and (2) DIC in pregnancy patients' data that included the following sections: a) clinical presentation of the patients; b)

laboratory parameters; c) pregnancy outcome; and d) long-term complications (Supplementary Material).

2.1 | Statistical analysis

Univariate analysis was used to test groups regarding maternal and fetal morbidities. We used the Shapiro-Wilk and Kolmogorov-Smirnov tests to determine data distribution. Categorical variables were analyzed using Pearson's chi-square test. Normally distributed quantitative variables were analyzed with either the *t*-test or 1-way ANOVA test. Not normally distributed quantitative variables were processed using the Mann-Whitney's test or the Kruskal-Wallis' test. Statistical significance was determined as a *P* value of <.05. The statistical analysis was performed using IBM Statistics SPSS 18.0 (SPSS Inc).

3 | RESULTS

3.1 | General description of the cohort

There were 145 data entries in the registry; 104 of them included patients' information. The epidemiology data were reported from 13 countries, of which 9 were from low- and middle-income countries (LMICs) and 4 were high-income countries (HICs). Physicians from 15 centers contributed to the registry data; the physicians practiced mainly in labor and delivery suites (*n* = 10) and maternal fetal medicine units (*n* = 5). The annual numbers of deliveries in the participating centers were divided into the following: <2000 deliveries (1 center), 2000 to 5000 deliveries (11 centers), 5000 to 10 000 deliveries (3 centers), and >10 000 deliveries (3 centers). The reported annual numbers of DIC cases per center were (1) <1 (16.6%; 3/18), (2) 1 to 10 (72.2%; 13/18), and (3) >10 cases (11.1%; 2/18). The number of DIC cases was related to the number of deliveries; only 2 centers reported more than 10 DIC cases annually, and both were from LMICs.

Patients' laboratory and clinical information were available from 104 patients. Both clinical and laboratory data were available in 94 cases from the following centers: 62.8% (59/94) from Soroka University Medical Center; 21.3% (20/94) from Universidad de los Andes; 14.9% (14/94) from Emek Medical Center; and 1.1% (1/94) from Universidad CEU Cardenal Herrera, Valencia, Spain. Clinical data were only available in additional 10 cases. The differences in the numbers of DIC cases per center reflect the size of their annual delivery volume; while Soroka University Medical Center handles >10 000 deliveries annually, both Universidad de los Andes and the Emek Medical Center handle 2000 to 5000 deliveries annually.

3.2 | Demographic characteristics

Table 1 presents the demographic characteristics of the study cohort. Mean maternal age is 31 ± 5.9 years, median gravidity was 4 (IQR, 2-7), and parity was 3 (IQR, 1-5). Ethnicity information was available for 95 patients: 63.2% (60/95) were Middle Eastern, 13.7% (13/95) were Caucasians, 2.1% (2/95) were Asian African and Hispanic each, and 16.8% (16/95) were with no defined ethnic origin. The median gestational age of delivery was 35 (IQR, 30.6-38.9) weeks. Mean birth weight was 2282.3 g ± 991.1 g.

TABLE 1 The demographic characteristics of the study cohort.

Demographic characteristics		
Maternal age (n = 94)		31 ± 5.9 y
Gravidity (n = 98)		4 (2-7)
Parity (n = 98)		3 (1-5)
Birth weight (n = 88)		2282.3 ± 991.1 g
Ethnicity	Middle Eastern	63.2% (60/95)
	Caucasians	13.7% (13/95)
	Asian African	2.1% (2/95)
	Hispanic	2.1% (2/95)
	No defined ethnic origin	16.8% (16/95)

Data are presented as percentage (number), median (25th-75th percentile), and mean ± SD.

3.3 | Clinical characteristics of women with DIC

The pregnancy complications associated with the development of DIC were as follows: the most frequent was placental abruption in 50% (52/104) of the patients, followed by stillbirth in 27.9% (29/104) of the cases; 89.7% (26/29) of stillbirth cases were associated with abruption. Other pregnancy complications included preeclampsia (21.2% [22/104]); preterm parturition (preterm labor and preterm PROM; 18.3% [19/104]); hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome (8.7% [9/104]); chorioamnionitis (2.9% [3/104]); and amniotic fluid embolism (0.96% [1/104]; Figure 1).

Data regarding the mode of delivery were available in 85.6% (89/104) of the patients included in the registry. Of them, 49 were delivered vaginally and 40 were delivered by cesarean section.

Postpartum DIC was reported in 61.5% (64/104) of cases, and the leading causes were (1) uterine atony (53.1% [34/64]); (2) placental accreta (23.4% [15/64]) and placenta previa (7.8% [5/64])—of note, there were 3 cases of combined placental accreta and placenta previa that were classified as placental accreta; (3) trauma to the birth canal (10.9% [7/64]); and (4) uterine rupture (4.6% [3/64]; Figure 2), all of which are known etiologies for PPH and subsequent DIC.

The differences in the antepartum and postpartum complications reported in patients with DIC differed among women from HICs to LMICs. The rate of abruption, stillbirth, and premature labor was higher among women with DIC in the HIC vs LMIC groups (Table 2). The leading pregnancy complications associated with DIC in HIC were placental abruption (66.2%), stillbirth (36.5%), preeclampsia (20.3%), and preterm labor (20.3%). In women from LMIC, the leading cause associated with DIC was preeclampsia (22.3%), followed by

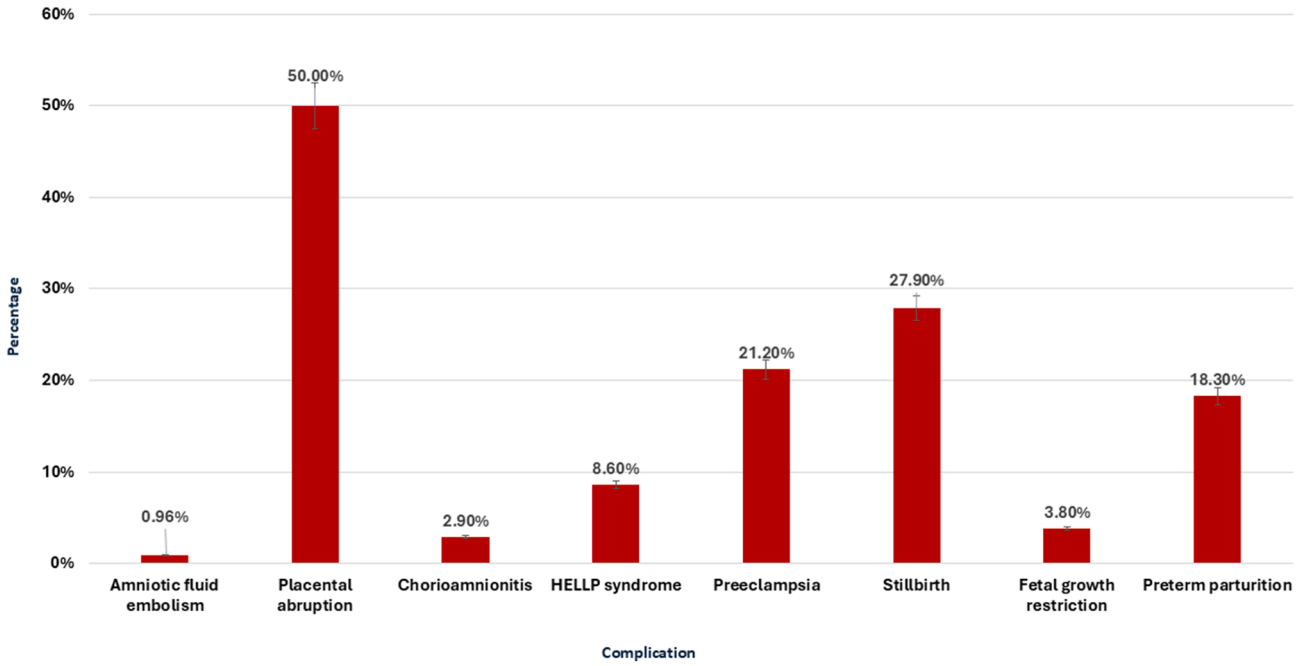

FIGURE 1 The distribution of pregnancy complications among patients with antepartum obstetrical hemorrhage. HELLP, hemolysis, elevated liver enzymes, and low platelet count.

placental abruption (10%), HELLP syndrome (6.7%), and stillbirth (6.7%; Table 2).

3.4 | Hemostatic studies

The median PT difference was longer, and fibrinogen concentration was lower among patients who had a positive pregnancy–specific DIC score at the first testing, upon diagnosis of DIC, and at the last test result available ($P < .001$ for all comparisons). Platelet counts were significantly lower among those with a positive pregnancy–specific DIC score, only at the first blood count test ($P < .001$). At diagnosis, those with a negative and positive pregnancy–specific DIC score had thrombocytopenia, but the difference was not significantly different. At the last test, both groups had a normal platelet count (Table 3).

We compared the hemostatic parameters between women with placental-mediated pregnancy complications (preeclampsia, HELLP

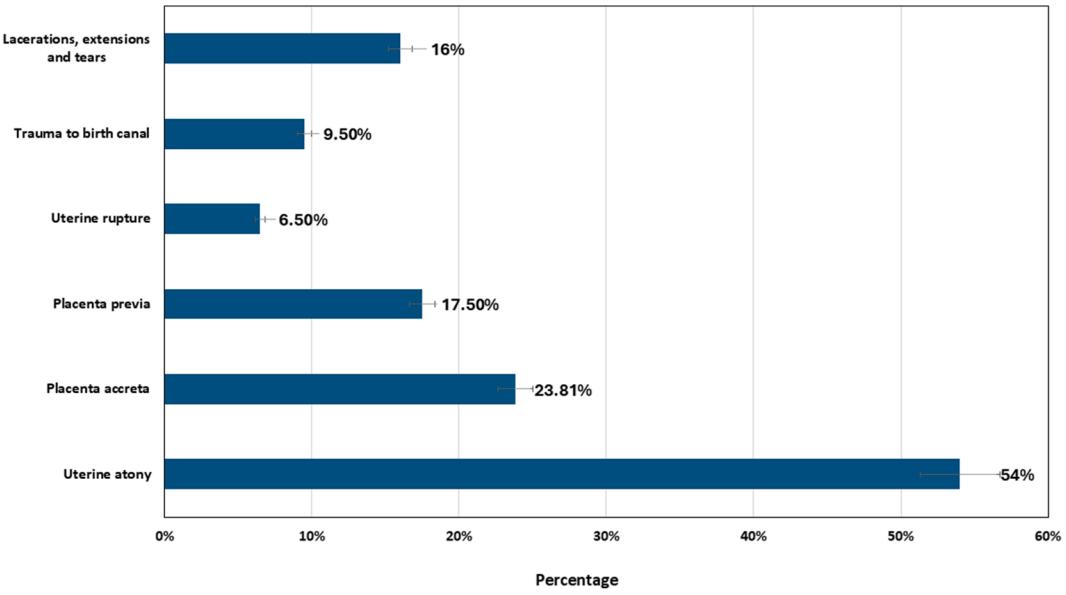

FIGURE 2 Etiologies and their distributions of peripartum complications leading to PPH and DIC. DIC, disseminated intravascular coagulation; PPH, postpartum hemorrhage.

TABLE 2 The distribution of pregnancy complications associated with DIC according to high- and low-income countries.

Timing of complications	Variable	High-income country (n = 74)	Low-income country (n = 30)	*P* value
Antepartum	Amniotic fluid embolism	0% (0/74)	3.3% (1/30)	.28
	Placental abruption	66.2% (49/74)	10% (3/30)	<.001
	Chorioamnionitis	2.7% (2/74)	3.3% (1/30)	>.99
	HELLP syndrome	9.5% (7/74)	6.7% (2/30)	>.99
	Preeclampsia	20.3% (15/74)	22.3% (7/30)	.79
	Stillbirth	36.5% (27/74)	6.7% (2/30)	.002
	FGR	5.4% (4/74)	0% (0/30)	.43
	Preterm PROM	4.1% (3/74)	3.3% (1/30)	>.99
	Preterm labor	20.3% (15/74)	0% (0/30)	.005
Postpartum	Liver hematoma	1.4% (1/74)	3.3% (1/30)	.5
	Liver rupture	1.4% (1/74)	3.3% (1/30)	.5
	Uterine atony	32.4% (24/74)	33.3% (10/30)	>.99
	Vaginal laceration	4.1% (3/74)	0% (0/30)	.555
	Uterine cervix tear	2.7% (2/74)	6.7% (2/30)	.577
	Uterine rupture	4.1% (3/74)	0% (0/30)	.555
	Placenta accrete	13.5% (10/74)	16.7% (5/30)	.76

Data are presented as percentage (cases/total).

DIC, disseminated intravascular coagulation; FGR, fetal growth restriction; HELLP, hemolysis, elevated liver enzymes, and low platelets; PROM, prelabor rupture of membranes.

syndrome, placental abruption, stillbirth, and fetal growth restriction) and those without such complications (Table 4). There were no differences in median platelet count, PT difference, and fibrinogen concentrations between the 2 groups. However, women without placental-mediated pregnancy complications had a higher median pregnancy–specific DIC score at diagnosis (P = .025) and at the last available test (P = .009) than those with placental mediated complication. Although there were no statistically significant differences in the different component of the DIC score, Figure 3 presents a trend in which women with placental mediated pregnancy complications had higher proportion of low platelet count (<50 000) at diagnosis and low fibrinogen (<300 mg/dL) at admission, while those without placental mediated pregnancy complications had higher proportion of prolong PT difference (>1.5 seconds) at admission and the last test and higher proportion of low fibrinogen at diagnosis and the last test available.

3.5 | Treatments

3.5.1 | Pharmacological and mechanical treatments for PPH

Oxytocin was the most common uterotonic agent that was administered to 76.9% (80/104) of the patients. Prostaglandins were administered to 41.3% (43/104) of them, 26 received $PGF_2\alpha$, and 24 received PGE_1/E_2 (Figure 4). Uterine tamponade was performed in 13.5% (14/104), Foley catheters were used in 10.6% (11/104), 1 patient had a Foley, and a Bakri balloon insertion, and 3 patients had uterine tamponade without mentioning the method.

3.5.2 | Surgical treatment for PPH

Among women with PPH and DIC, 11.5% (12/104) required suture of vaginal and surgical lacerations and 11.5% (12/104) needed uterine hemostatic suture, while 13.5% (14/104) needed ligation of the uterine artery, 16.3% (17/104) had internal iliac artery ligation, and 25% (26/104) underwent hysterectomy. Among those who delivered vaginally, 8 women needed an explorative laparotomy, while 14 patients required relaparotomy following cesarean section.

3.5.3 | Blood products transfusion

More than 4 packed cells were administered to 29.8% (31/104) of cases, 34.6% (36/104) received more than 4 fresh frozen plasma units, 10.6% (11/104) received more than 10 units of cryoprecipitate, and 4.8% (5/104) received more than 10 units of platelets (Figure 5).

TABLE 3 Hemostatic parameters of women with and without DIC (according to the pregnancy-specific DIC score) during hospitalization.

	First test			Diagnosis			Last sample		
	Without DIC (n = 9)	With DIC (n = 72)	*P* value	Without DIC (n = 9)	With DIC (n = 72)	*P* value	Without DIC (n = 9)	With DIC (n = 72)	*P* value
PT difference (s)	−0.25 (−2.7 to 3.4)	3.2 (0-18)	<.001	0.1 (−1.9 to 5.3)	5 (2.7-99)	<.001	0 (−2.7 to 4)	2.12 (0.8-33.2)	<.001
Fibrinogen (mg/dL)	469 (77-723)	166 (0-425)	<.001	417 (107-539)	145.5 (0-386)	<.001	531.5 (100-815)	294 (0-573)	<.001
Platelets (103/μL)	226 (57-398)	161 (62-313)	<.001	137 (61-283)	112.5 (14-267)	.1	190 (10-905)	159 (59-630)	.1

DIC was defined according to the pregnancy-specific DIC score [16] (median [25th-75th percentile]); PT difference was calculated as PT value of the patient − laboratory control.
DIC, disseminated intravascular coagulation.

3.5.4 | Long-term maternal complications

There were 3 cases (2.8%) of maternal death, renal failure was observed in 9.6% (10/104) of the cohort, thrombotic complications and respiratory failure were reported each in 2.8% (3/104) of the patients, and 1.9% (2/104) had liver failure and multiorgan failure.

4 | DISCUSSION

This study presents the results of the first International DIC Registry in pregnancy. This is a collaborative effort of the Scientific and standardization committees for Women's Health Issues in thrombosis and hemostasis and DIC of the ISTH and the participating departments. This registry includes the clinical and laboratory data of the largest cohort of pregnant women with DIC worldwide. The principal findings of our study are as follows: (1) placental abruption is the leading cause for antepartum and intrapartum DIC, especially when associated with stillbirth—the leading etiology for postpartum DIC was uterine atony, especially following/during caesarean sections; (2) the contribution of abnormally implanted placenta (ie, placenta accreta and/or previa) for the development of DIC is increasing; (3) the leading pregnancy complications associated with DIC were placental abruption in HIC and preeclampsia in LMIC; (4) hemostatic parameters differed between women who had a positive pregnancy–specific DIC score and those who did not meet that criteria; and (5) women with placental-mediated pregnancy complications had lower median pregnancy–specific DIC scores than those without such complications at the time of diagnosis of DIC and following recovery, suggesting a different mechanism of disease in the 2 groups.

4.1 | Etiologies of DIC—a global perspective

The rate of severe obstetrical hemorrhage is steadily increasing in HIC [24,25], and its decline in the LMIC has recently plateaued [26,27]. The increase in the rate of uterine atony [28], abnormally invasive placenta [29], and retained placenta requiring manual removal [30] are the leading etiologies contributing to these observations. Our study is among the few reports differentiating between antepartum and postpartum obstetrical hemorrhage leading to DIC [31,32]. This difference is important as the timing of the bleeding may be related to different underlying mechanisms leading to obstetrical hemorrhage and DIC [33].

Placental abruption is the leading etiology for DIC in women with antepartum bleeding. This is in accord with previous reports [15,34–37] suggesting the strong association between placental abruption and maternal DIC. Moreover, the combination of stillbirth and placental abruption is a prominent cause of DIC; indeed, 89.7% of stillbirth cases leading to DIC were associated with abruption, and they comprised 56.5% of all abruption cases leading to maternal DIC, further supporting the common perception that if the abruption is severe enough to cause fetal death, it is more likely to also lead to

TABLE 4 Hemostatic difference between women with DIC with and without placental-mediated pregnancy complication.

Hemostatic parameter	Timing of testing	With placental-mediated pregnancy complication (n = 65)	Without placental-mediated pregnancy complication (n = 39)	*P* value
Platelet count (103/μL)	First available	186 (140.8-245.5)	180 (102-233)	.17
	Diagnosis	127.5 (85.5-159.5)	101 (76-135)	.07
	Last available	189 (139-232)	138 (108-233)	.29
PT difference (s)	First available	1 (−0.3 to 3.2)	1.8250 (0-3.4)	.41
	Diagnosis	3.6 (1.5-7.6)	4.05 (2.1-6.9)	.92
	Last available	0 (0.88-1)	0.1 (−0.5 to 1.7)	.35
Fibrinogen (mg/dL)	First available	244 (138-480.75)	325 (162.5-432)	.73
	Diagnosis	153 (90.8-206)	153 (122-208)	.57
	Last available	504.5 (412.3-623.8)	479 (289.5-570.5)	.12
DIC according to pregnancy-specific DIC score	First available	31 (2-51)	27 (12.5-51))	.37
	Diagnosis	51 (38-51)	51 (51-52)	.025
	Last available	3.5 (0-25)	19.5 (5-27)	.009

Data are presented as median (25th-75th percentile).

DIC, disseminated intravascular coagulation.

maternal death. Moreover, placental abruption and stillbirth were the leading pregnancy complications associated with DIC in HIC. This suggests that with a high level of prenatal care, the relative contribution of acute events such as placental abruption is gaining more prominence. The prevention of such low prevalence events is challenging. Placental abruption is also involved in the development of DIC among women with HELLP syndrome [36]. This was a surprising observation as the previous perception was that the driving forces to DIC in HELLP syndrome were the perturbation in the liver cellular function associated with this complication [21,38].

Preeclampsia was the third leading cause of antepartum DIC, followed by HELLP syndrome and chorioamnionitis. This observation is novel, as prior reports [15,36,38–41] suggested that most cases of DIC in women with hypertensive disorders of pregnancy were related to HELLP syndrome rather than preeclampsia. However, evidence of increased thrombin generation in women with

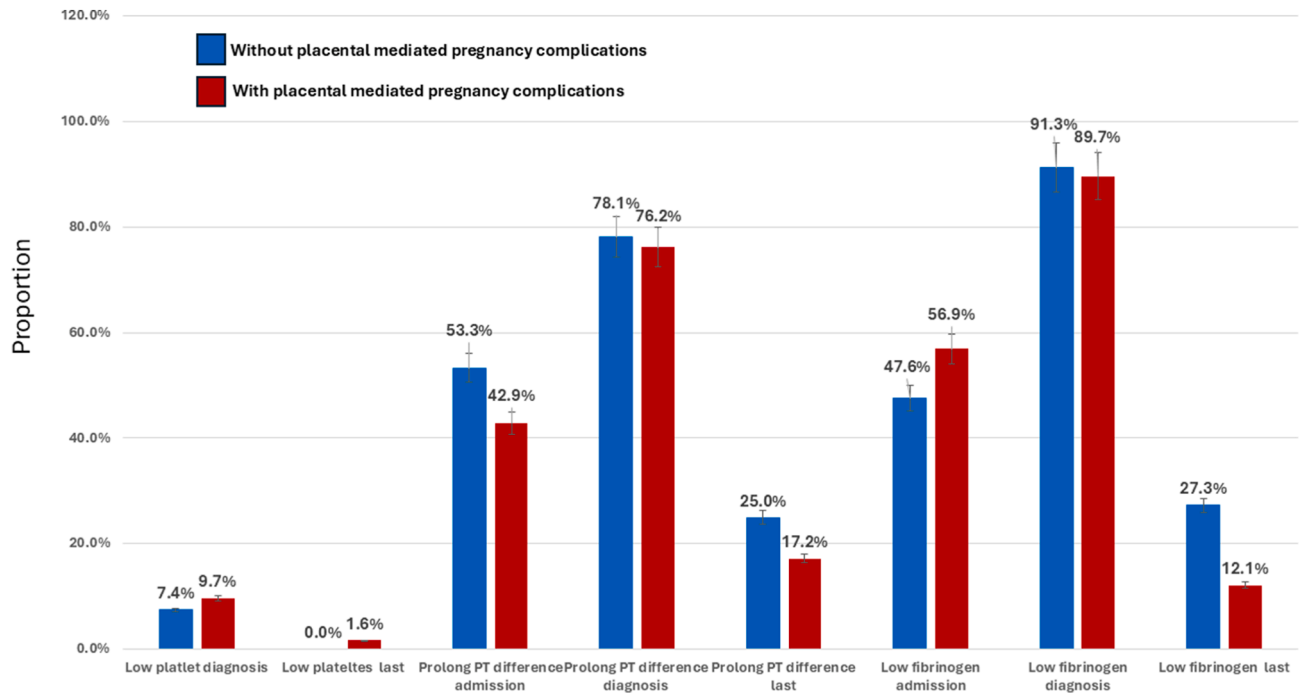

FIGURE 3 The rate of severe hemostatic parameters of the pregnancy-specific DIC score in women with and without placental-mediated pregnancy complications. PT, prothrombin time.

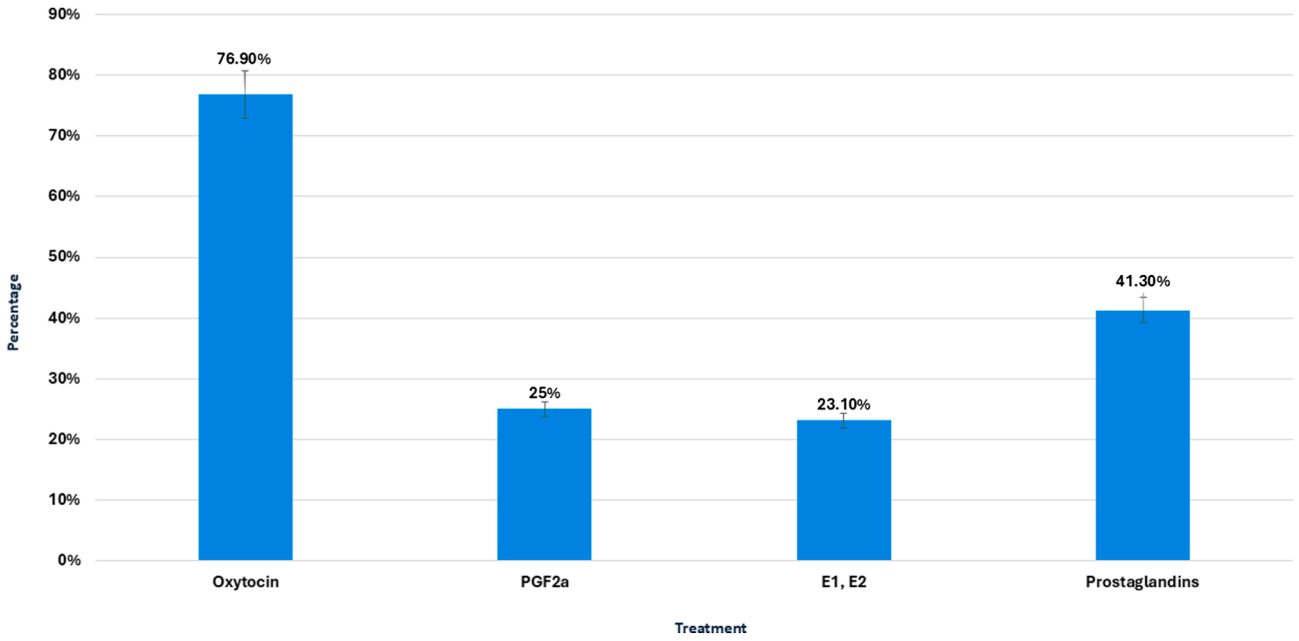

FIGURE 4 The distribution of pharmacological treatments for obstetrical hemorrhage among women with DIC. DIC, disseminated intravascular coagulation.

preeclampsia [42–44] further supports the increased risk for DIC, especially in cases that were diagnosed late. Indeed, in HICs, it is mainly HELLP syndrome, especially when complicated with abruption, that contributes to the development of DIC [1,15,16]. However, in these countries, although preeclampsia is often associated with abruption, the rate of DIC among women with this syndrome is low. Nevertheless, this is not the case in LMIC, where preeclampsia is often diagnosed very late and therefore associated with the development of DIC [45]. Indeed, our findings support this view and preeclampsia was the leading pregnancy complication associated with HELLP syndrome in women from LMIC who were included in this registry. The multicentric nature of this registry helps us to represent and validate previous observations regarding the diversity in pregnancy complications associated with DIC in HIC and LMIC. This

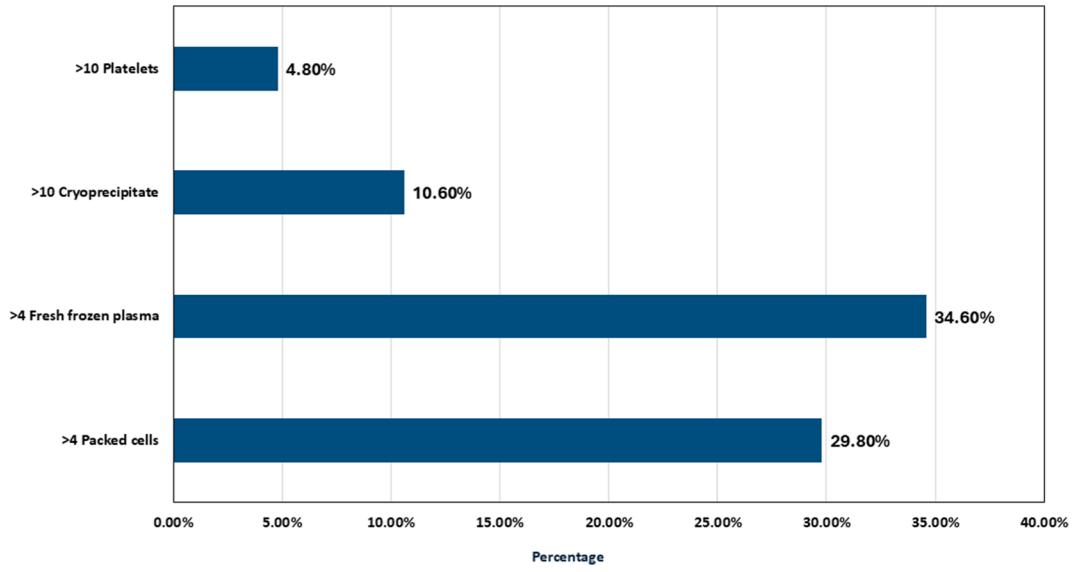

FIGURE 5 The distribution of massive blood product administration among women with DIC. DIC, disseminated intravascular coagulation.

information is important for prenatal care counseling and prevention programs aiming to reduce maternal morbidity and mortality resulting from obstetrical hemorrhage.

The presence of preterm parturition in 18.3% of the DIC cases is a novel observation of this registry. Preterm parturition, either as spontaneous preterm labor or preterm PROM, is not by itself a cause for DIC. Nevertheless, the complications of spontaneous preterm parturition, such as chorioamnionitis, sepsis [46–48], and abruption, are associated with the development of DIC. Indeed, in a case series of women with suspected amniotic fluid embolism that eventually turned out to be acute maternal systemic inflammatory response and sepsis, the patients developed DIC [49]. We have only one case with amniotic fluid embolism in this registry, representing the rarity of this event and its low contribution to the overall prevalence of maternal DIC.

Severe PPH due to uterine atony is the leading cause of postpartum DIC in this registry, mainly during or after cesarean deliveries, which is in accord with previous reports [15,50]. Indeed, the increasing rate of cesarean sections [51] is one of the explanations suggested for the higher incidence of uterine atony in HICs. Furthermore, the higher frequency of cesarean deliveries contributes to the increasing rate of abnormally invasive placentation [52] that is the second leading cause for PPH complicated postpartum DIC in this registry, either as an isolated problem or in combination with placenta previa. The combined pathology of placenta previa-accreta carries an increased risk for substantial hemorrhage due to its adjacency to the major uterine vessels and organs such as the urinary bladder [53]. Indeed, these surgeries are accompanied by severe maternal hemorrhage, often necessitating hysterectomy, and result in severe maternal morbidity and mortality [54,55]. With the increase in the prevalence of placenta accreta in the past decades, we also observed its higher contribution to the development of DIC, increasing from 6.5% in Rattray's report [15] to 23.4% in our registry, which is in accord with a similar report from China [56]. The contribution of birth canal laceration to obstetrical hemorrhage leading to DIC was relatively low in our registry.

4.2 | Hemostatic changes in the different causes of DIC in pregnancy

This registry allows a unique observation regarding the changes in the hemostatic laboratory parameters during DIC. Indeed, women with a positive obstetrical DIC score had a lower median of PT difference and fibrinogen concentration at the first testing than those with a negative DIC score result. This was the observation at the time of the diagnosis of DIC and at the last test result available, suggesting that those who did not meet the criteria of pregnancy-specific DIC score may have suffered from severe obstetrical hemorrhage but did not have DIC. On the other hand, platelet count had a low diagnostic contribution in the hemostatic assessment of DIC. Indeed, platelet count was lower among women with a positive DIC score only at the first blood count. These observations can be explained by the fact that some of the pregnancy complications associated with DIC have thrombocytopenia that may not be related to DIC itself. On the other hand, the effect of low fibrinogen and prolongation of PT is essential to the diagnosis of DIC and properly represents the degree of hemostatic failure associated with DIC. These findings further validate the utility of the pregnancy-specific DIC score in the diagnosis of patients with a high probability of DIC. Moreover, when we compare the rate of positive pregnancy–specific DIC score between HIC and LMIC centers, the difference was not significant, suggesting that the score is relevant and has high external validity.

We further investigated the hemostatic differences between women with DIC with and without placental-mediated pregnancy complications. The rationale for this comparison was the notion that the different etiologies for DIC may have a unique coagulation profile. However, we found no difference in the median platelet count, PT difference, and fibrinogen concentration at admission, diagnosis, and the last test available.

We had very few reports of point-of-care viscoelastic testing in this registry; therefore, we could not use the data to study the impact of the different testing methods in the diagnosis and management of DIC in pregnancy. Since this is an evolving field, we hope that future data collection will allow a better understanding of the role and impact of these tests in obstetrical DIC.

4.3 | Complications of DIC in pregnancy

This registry is the first to present the overall maternal complications associated with DIC in pregnancy in such a large cohort of patients. Hysterectomy complicates 25% of DIC cases. The major contributing factor for this observation is placenta accreta (15/26) followed by failure to achieve hemostasis by uterine and pelvic blood vessel ligations and massive blood transfusion. Of note, local practices also affect the decision to perform a hysterectomy. Indeed, in a pan-European cohort of women who had severe obstetrical hemorrhage, in some countries, hysterectomy was performed only after massive blood transfusion, while in others, the removal of the uterus was performed at early stages of the management of severe obstetrical hemorrhage [57]. Similarly, a substantial proportion of women with DIC in pregnancy required uterine and internal iliac artery ligation.

4.4 | What have we learned from our registry?

This is the first international registry of women with DIC in pregnancy. The diagnosis of DIC was clinical, and diagnostic scores were not used by the contributing centers. Indeed, upon admission, only 50% of the cases met the criteria of DIC based on the pregnancy-specific DIC scoring system, further emphasizing the need for such a score to improve the diagnostic accuracy of these patients.

The contribution of placental abruption to DIC is evident from all the centers included in the registry. It is the most important

pregnancy complication that leads to DIC, especially in the presence of fetal death [15]. Thus, intensive observation and management of such patients, even if they seem hemodynamically stable, is needed. A second lesson from this registry is the need to develop prediction and risk assessment models for placental abruption and stillbirth that will enable planning future preventive interventions. Indeed, a previous report [58] suggested that the ratio of angiogenic and antiangiogenic factors at 24 to 28 weeks of gestation can identify 80% of women with subsequent fetal death and placental vascular malperfusion. Introducing such screening methods into the clinical routine may also assist in identifying women at risk for placental abruption and lead to earlier intervention that will prevent this ominous combination of abruption and stillbirth. However, such an intervention will need a large multinational trial to have sufficient power to demonstrate clinical utility.

Uterine atony is the leading cause for PPH; this observation is in accord with previous reports [59]. However, the data from this registry highlights the sentinel contribution of cesarean deliveries to the development of atony-related life-threatening PPH associated with DIC. This observation can be attributed to the underlying pathology leading to cesarean delivery, including chorioamnionitis, labor dystocia, and placenta accreta spectrum.

We further compared the pregnancy-specific DIC score results between the 2 groups; those without placental-mediated pregnancy complications had a higher median pregnancy-specific DIC score at diagnosis and the last available test than those with such complications. Furthermore, we compared the frequency of low platelet count ($<50\ 000 \times 10^3/\mu L$), low fibrinogen concentration (<300 mg/dL), and prolonged PT difference (>1.5 seconds) between pregnant patients with DIC with and without placental-mediated complications at the 3-measurement point. Although comparisons were not statistically different, they demonstrated a clear trend that may explain the observed differences in the pregnancy-specific DIC score between the groups. Women with placental-mediated pregnancy complications had a higher rate of low fibrinogen at admission and a higher rate of low platelet count at diagnosis, while women without placental-mediated pregnancy complications had a higher rate of prolonged PT difference in all testing points and a higher rate of low fibrinogen at diagnosis and the last available test. Collectively, these findings suggest that women with placental-mediated pregnancy complications who develop DIC have increased thrombin generation [21,42,43,60–64] and fibrinolysis [65–67] that recover promptly following the resolution of their pregnancy complication (ie, delivery and administration of blood product). Our observation is in accord with the recent report [68]. On the other hand, those without placental-mediated pregnancy complications have a hemostatic problem that results from consumption coagulopathy that is first observed in the perturbation of their PT results, and when their coagulopathy further escalates, we observe the low fibrinogen concentrations that increase the severity of coagulopathy, resulting in a slower recovery. Our observation suggests that attending DIC resulting from placental-mediated pregnancy complications (placental abruption, preeclampsia, and HELLP syndrome) may require a different approach than that resulting from uterine atony or placenta accreta.

4.5 | Strengths and limitations of our study

The limitations of our study include its retrospective nature, the differences in the clinical diagnosis of DIC in the participating centers, and the different management algorithms. Moreover, due to the scrutiny and extended clinical data collection done in this registry, many have chosen just to answer the general epidemiological section (ie, regarding the number of deliveries and DIC cases per year) rather than go deep into the cases and collect all the laboratory and clinical information we wanted to include in the registry. We acknowledge the lack of sufficient data on point-of-care testing such as ROTEM and TEG. These are important tools in tailoring the hemostatic support during DIC in pregnancy; however, our registry presents real-world data, and in the majority of obstetrical departments, these tests are not in routine use. Nevertheless, despite this weakness, it is the largest data set thus far on maternal DIC and its implications. Given the rarity of DIC, we foresee that studies with a similar conceptual approach will have to be based on large EMR records data sets that will be fused. These are inherent limitations of an international registry. However, the registry data still actually contribute to the study as they serve to identify gaps between the different practices and to set the stage for developing a common language, direct the relevant research questions, and contribute to the study as they serve to identify gaps between the different practices and to set the stage for a common language and relevant research questions.

5 | CONCLUSIONS

DIC in pregnancy is a severe maternal morbidity that is associated with short- and long-term complications. Women who met the criteria of the pregnancy-specific DIC score had a more severe coagulopathy than those who did not meet them. Thus, our registry emphasizes the need for a common language in terms of diagnostic criteria and utilization of diagnostic scores. Moreover, our findings further emphasize the important role of cesarean section and low platelet count in PPH, requiring further studies on the risk factors for PPH and DIC in cesarean deliveries, and functional platelet contribution to the development of DIC in women with PPH.

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ETHICS STATEMENT

The study was approved by the local institutional review boards of the participating centers.

AUTHOR CONTRIBUTIONS

O.E., M.O., R.A.K., T.I., R.S., E.S., and J.T. contributed to the conception of this study. O.E., L.B., M.O., R.A.K., and J.T. designed this study. O.E., L.B., A.D.S., S.I., and B.Q. contributed to data collection. O.E. and J.T. contributed to analysis of the study. O.E., L.B., A.D.S., S.I., B.Q., M.O., R.A.K., T.I., R.S., E.S., and J.T. contributed to the drafting of the manuscript.

DECLARATION OF COMPETING INTERESTS

There are no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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