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Original Article

Treatment Outcomes of Anticoagulant Therapy and Temporary Inferior Vena Cava Filter Implantation for Pregnancy Complicated by Venous Thrombosis

Nobuhiro Hara, MD,[1] Takamichi Miyamoto, MD,[2] Junji Yamaguchi, MD,[1] Takamasa Iwai, MD,[1] Sadahiro Hijikata, MD,[1] Keita Watanabe, MD,[1] Yuichiro Sagawa, MD,[1] Ryo Masuda, MD,[1] Ryoichi Miyazaki, MD,[1] Naoyuki Miwa, MD,[1] Masahiro Sekigawa, MD,[1] Tetsuo Yamaguchi, MD,[1] Yasutoshi Nagata, MD,[1] Toshihiro Nozato, MD,[1] Orie Kobayashi, MD,[3] Satoshi Umezawa, MD,[3] and Toru Obayashi, MD[1,4]

Objective: Although deep vein thrombosis (DVT) followed by pulmonary thromboembolism (PE) is a critical complication during pregnancy, there have been few reports about its intrapartum management. We evaluated intrapartum management by using a temporary inferior vena cava filter (IVCF) in pregnant women with PE/DVT.

Materials and Methods: Eleven women with PE/DVT during pregnancy between January 2004 and December 2016 were included. The patients were hospitalized for intravenous unfractionated heparin infusion after acute PE/DVT onset. Seven patients were discharged and continued treatment with subcutaneous injection of heparin at the outpatient unit. IVCF was implanted 1–3 days before delivery in 10 patients. Anticoagulant therapy was discontinued 6–12 h before delivery. We retrospectively analyzed rates of maternal or perinatal death, and recurrence of symptomatic PE/DVT.

Results: One patient was diagnosed as having PE/DVT and 10 had DVT alone. One patient suffered hemorrhagic shock during delivery; however, maternal or perinatal death and recurrence of symptomatic PE/DVT did not occur in any patient.

Conclusion: Maternal or perinatal death and recurrence of symptomatic PE/DVT was not seen in women diagnosed as having PE/DVT during pregnancy and treated with anticoagulant therapy and IVCF.

Keywords: deep vein thrombosis, pregnancy, inferior vena cava filter, pulmonary thromboembolism

[1] *Department of Cardiology, Japanese Red Cross Musashino Hospital, Tokyo, Japan*
[2] *Department of General Medicine, Japanese Red Cross Musashino Hospital, Tokyo, Japan*
[3] *Department of Gynecology and Obstetrics, Japanese Red Cross Musashino Hospital, Tokyo, Japan*
[4] *Department of Clinical Engineering, Gunma Paz College, Gunma, Japan*

Received: September 27, 2017; Accepted: January 12, 2018
Corresponding author: Nobuhiro Hara, MD. Department of Cardiology, Japanese Red Cross Musashino Hospital, 1-26-1 Kyonan-cho, Musashino, Tokyo 180-8610, Japan
Tel: +81-422-32-3111, Fax: +81-422-32-3130
E-mail: hara-nobuhiro@hotmail.co.jp

Introduction

An association between pregnancy and venous thrombosis was reported in 1965.[1)] Deep vein thrombosis (DVT) followed by pulmonary thromboembolism (PE) is a critical problem during pregnancy and has been reported to be one of the major causes of death in pregnant women.[2–4)] During the perinatal period, DVT occurs because of (1) increased blood coagulation function, hypofibrinolysis, and platelet activation; (2) venous smooth muscle relaxation due to estrogen; (3) compression of the iliac vein and inferior vena cava by the gravid uterus; and (4) blood congestion following delivery or cesarean section, injury due to delivery or cesarean, and postpartum recuperation in bed.[5)]

Pregnant females have a 4- to 5-fold higher risk of PE/DVT than that of non-pregnant women of the same age.[6)] It has been reported that PE/DVT during the perinatal period in Japan has increased 6.5 times in the last decade.[7)] The incidence of PE/DVT at 1.2/1,000 deliveries is higher after delivery than during pregnancy and appears to increase with age.[8)] Mortality from PE/DVT associated with pregnancy has been reported to be 0%–1.91%.[8)]

Although the risk of thrombotic events in pregnancy is relatively low, the severity of the condition and its adverse effect on the health of women and outcomes of pregnancy is enormous.[9] However, the choice of treatment options for PE/DVT in pregnancy is limited, and the treatment is controversial.[10]

We believe it is necessary to consider perinatal management of patients who develop venous thromboembolism (VTE) during pregnancy. The purpose of this study was to evaluate intrapartum management by using an inferior vena cava filter (IVCF) in pregnant women with PE/DVT.

Materials and Methods

Patient population

A total of 15,560 pregnant women gave birth at our hospital between January 2004 and December 2016. A series of 11 pregnant women who developed symptomatic PE/DVT during pregnancy were included in this study. These patients were diagnosed as having venous thrombosis from computed tomography (CT) scan images or ultrasound images of veins of the lower extremities. In cases with only lower limb symptoms, contrast CT was not performed if electrocardiography and echocardiography showed no right heart overload. The onset was defined as early (before 16-weeks of pregnancy), mid (from 16th to 27th week of pregnancy), and late (28th week of pregnancy or later) pregnancy. For the treatment of acute thrombosis, all patients were hospitalized and received intravenous infusion of unfractionated heparin, with the goal of achieving an activated partial thromboplastin time (aPTT) of 1.5 to 2 times above normal (26–36 seconds). Treatment was administered on the basis of the clinical symptoms, D-dimer level (within normal limits of 0.5 μg/mL), and echocardiography of the veins of lower extremities. Patients who were on ambulatory treatment and discharged were shifted to subcutaneous administration of heparin. Patients recruited before January 2012 could not perform self-injection of subcutaneous heparin, so it was administered at the hospital once a day. After January 2012, for patients covered by health insurance, subcutaneous self-injection was administered twice a day. Anticoagulation therapy was planned to be discontinued 6–12 h before the expected delivery. Patients who underwent heparin therapy in the outpatient unit were hospitalized 3–4 days before the expected due date. An IVCF was inserted 1–2 days before the expected delivery. The IVCF (New House Protect, Toray, Ltd., Chiba, Japan) was used. A method of childbirth (transvaginal or cesarean) was chosen on the basis of the obstetrical indication at the discretion of the obstetrician. After no bleeding complications were confirmed, heparin was resumed and replaced by warfarin. IVCF was removed when anticoagulation therapy was resumed, and the patient was able to leave the bed.

Follow-up

We retrospectively analyzed rates of maternal or perinatal death and recurrence of symptomatic PE/DVT.

Statistical analysis

All continuous variables are presented as means ± standard deviations (SDs), and dichotomous data are shown as percentages. Statistical analysis was performed by using Microsoft Excel statistics software, ver. 2012.

Ethics

This study conformed to the ethical principles of the Declaration of Helsinki. The requirement for informed consent was waived because all data were cataloged anonymously. The institutional review board of the Japanese Red Cross Musashino Hospital approved the study's protocol. The information disclosure document associated with this study is available on the hospital's website. Patients were notified about their participation in the study and informed that they were free to opt out of study participation at any time.

Results

Demographic and clinical data of the subjects are shown in **Table 1**. One (9.1%) patient (case 4) had a thrombotic risk factor caused by antiphospholipid antibody syndrome (**Tables 2–4**). PE was diagnosed in one patient with a complaint of dyspnea who was subjected to contrast-enhanced CT following a right heart overload visible on electrocardiography and echocardiography. For other cases, throm-

Table 1 Patient characteristics at baseline

Age, years		35±5
Body weight, kg		57±12
Creatinine, mg/dL		0.42±0.05
Blood cell counts	RBC, ×10⁴/μL	367±20
	Ht, %	33.3±2.6
	Hb, g/dL	11.3±0.9
	WBC, /μL	9130±2010
	Plt, ×10⁴/μL	23.9±7.7
DVT with PE (%)		1 (9.1)
DVT without PE (%)		10 (90.9)
Thrombophilic diathesis (%)		1 (9.1)

The number of patients was 11. Values are means±standard deviations (SDs) or n (%). All continuous variables are presented as means±SDs, and dichotomous data are shown as percentages. RBC: red blood cell count; Ht: hematocrit; Hb: hemoglobin; WBC: white blood cell count; Plt: platelet count; PE: pulmonary thromboembolism; DVT: deep vein thrombosis

Table 2 The data of onset of PE/DVT

Case	Age (year)	BMI (kg/m^2)	Birth experience	PE	DVT	Left or right	Site	Gestational weeks at PE/DVT onset	D-dimer (μg/mL)
1	28	22.4	Primipara	−	+	L	Femoral	10	6.4
2	33	22.4	Multipara	−	+	R	Femoral	32	3.1
3	31	26.4	Primipara	−	+	L	Femoral	25	3.9
4	39	21.3	Primipara	−	+	L	Femoral	22	3.3
5	39	24.1	Multipara	−	+	L	Ilio-femoral	28	2.3
6	40	26.2	Multipara	−	+	L	Femoral	12	27.0
7	40	22.3	Primipara	+	+	R	Femoral	29	6.1
8	40	22.9	Primipara	−	+	L	Ilio-femoral	32	3.3
9	31	21.1	Primipara	−	+	L	Ilio-femoral	16	2.5
10	26	26.4	Primipara	−	+	L	Ilio-femoral	26	2.3
11	32	23.2	Primipara	−	+	L	Ilio-femoral	28	8.3

Mass index. The normal D-dimer value is ≤0.5 μg/mL. PE: pulmonary thromboembolism; DVT: deep vein thrombosis; L: left; R: right; BMI: body mass index

Table 3 Treatment course before delivery

Case	Injection methods after intravenous infusion	TTR (%)	aPTT before delivery (second)	D-dimer before delivery (μg/mL)	Echography just before delivery
1	Visited the hospital once a day	50	33.7	2.1	Not performed
2	Visited the hospital once a day	0	27.8	3.1	Femoral
3	Continued intravenous infusion	0	34.4	2.3	Femoral
4	Visited the hospital once a day	0	28.8	1.3	Femoral
5	Continued intravenous infusion	67	30.9	1.9	Not performed
6	Visited the hospital once a day	50	35.1	2.0	Femoral
7	Visited the hospital once a day	50	38.3	3.9	Not performed
8	Continued intravenous infusion	80	39.6	3.2	Not performed
9	Continued intravenous infusion	50	39.6	0.9	Not performed
10	Subcutaneous self-injection	33	31.2	0.9	Ilio-femoral
11	Subcutaneous self-injection	38	37.5	2.0	Not performed

The normal aPTT value is 26–36 seconds. The normal D-dimer value is ≤0.5 μg/mL. TTR: time in therapeutic range; aPTT: activated partial thromboplastin time

Table 4 Treatment course of birth date and after delivery

Case	Weeks at delivery	Mode of delivery	Transfusion	Resume heparin after delivery (day)	IVCF	Placement timing before delivery (day)	Retrieval timing after delivery (day)	Captured thrombus
1	38	VD	−	1	−			
2	39	VD	−	1	+	1	2	+
3	37	CS	−	1	+	1	2	+
4	37	CS	−	3	+	1	4	+
5	37	VD	−	3	+	1	4	+
6	38	CS	−	3	+	0	4	+
7	31	CS	−	1	+	13	1	+
8	33	CS	−	2	+	0	3	−
9	31	VD	−	2	+	3	3	+
10	37	VD	−	1	+	1	1	+
11	37	VD	+	4	+	2	5	+

VD: vaginal delivery; CS: cesarian section; IVCF: inferior vena cava filter

bosis was diagnosed by echocardiography of the lower extremities without respiratory symptoms.

Table 2 shows the data of patients with venous thrombosis, which was diagnosed during early, mid, and late pregnancy in two, four, and five patients, respectively. Eight women were primiparas, and none of the pregnant women had a history of PE/DVT. DVT was found on the left side in nine (81.8%) patients, and D-dimer was elevated in all patients.

Table 3 shows the patients' treatment course before delivery. For the treatment of acute thrombosis, all patients were hospitalized and received intravenous infusion of unfractionated heparin. Of the patients who developed PE/DVT during late pregnancy, four patients (cases 3, 5, 8, and 9) continued hospitalization until childbirth for intravenous infusion of unfractionated heparin. Other patients were hospitalized during the acute phase for intravenous heparin administration and subsequently discharged with a recommendation for subcutaneous administration of heparin. Five patients (cases 1, 2, 4, 6, and 7) were unable to self-administer subcutaneous heparin and visited the hospital once a day for the same. Two patients (cases 10 and 11) self-administered subcutaneous heparin after discharge. The time in the therapeutic range of heparin between the diagnosis of venous thrombosis and delivery was $<50\%$ in nine (81.8%) patients. aPTT level just before delivery was either at the target value or less.

For D-dimer level just before delivery, only one patient (case 2) maintained the same level as that recorded during onset, whereas the others showed levels lower than the previous level. However, overall, the levels of all patients were higher than normal. Five patients underwent echosonography of the veins of the lower extremities before delivery, and it was seen that the thrombus remained in the proximal deep vein.

Table 4 shows the treatment course data in the peri- and postnatal periods. The route of delivery was cesarean section ($n=6$) or vaginal delivery ($n=5$). Although it was planned to implant IVCF in all patients, it could not be inserted in one patient in whom labor had already started (case 1). One patient who developed PE (case 7) was implanted with IVCF in the acute phase. In nine patients, the IVCF was inserted 0–3 days before the expected due date. All patients receiving placement of an IVCF underwent suprarenal implantation. Anticoagulant therapy was resumed 1 to 4 days after delivery, and IVCF was removed 1 to 5 days after delivery (mean, 2.9 days). At the time of IVCF removal, nine (90.0%) patients had a captured thrombus. The captured thrombi of four patients (cases 4, 6, 7, and 11) were >1 cm in diameter.

Complications associated with IVCF were not observed. There was no maternal or perinatal death, and the recurrence of symptomatic PE/DVT was associated with short-term discontinuation of anticoagulant therapy and use of IVCF. One patient had a systolic blood pressure of 60 mmHg, developed hemorrhagic shock due to delivery, and required emergency transfusion. All patients resumed treatment with heparin and then switched to warfarin after delivery. Three patients discontinued taking warfarin within 3 months, three within 1 year, and five took warfarin for >1 year; no complications were reported for any of the patients.

Discussion

Anticoagulation for VTE related to pregnancy

Anticoagulant therapy is the gold standard for venous thrombosis. However, warfarin is known to cross the placenta and there are reports of chondrodysplasia, such as dyschondroplasia, nervous system abnormalities, and death associated with bleeding tendency in fetuses.[11] Recently, the benefits direct oral anticoagulants (DOACs) for venous thrombosis have been reported.[12] However, although placental transfer of DOACs has been found, their safety has not been established. Consequently, treatment with heparin is primarily provided for pregnant women who develop PE/DVT. Low-molecular-weight heparin is the preferred therapy for acute VTE that occurs during pregnancy.[13] However, its use is not permitted in Japan. Therefore, administration of unfractionated heparin is the standard therapy for VTE that occurs during pregnancy. However, it is difficult to continue effective anticoagulation therapy. During pregnancy because heparin metabolism can change, heparin blood levels can be low, and its duration of action may decrease, with subsequent dose adjustments becoming more difficult than usual.[14] It has been reported that the size of the thrombus increased even after the use of heparin.[15] In our results, the aPTT value just before delivery was in the normal range or less in all patients. In addition, anticoagulant therapy must be discontinued despite the high risk of thrombosis at delivery. The use of heparin at delivery is risky because of bleeding at birth. According to a report by Patterson et al., the incidence of blood transfusion during pregnancy was 1.4%, of which $\geq 90\%$ was during the delivery.[16] According to the Perinatal Committee of the Japan Society of Obstetrics and Gynecology in 2008, 90% of intrapartum bleeding occurs in vaginal deliveries (800 mL) and in cesarean section (1,500 mL; includes amniotic fluid). In our study, anticoagulation therapy was discontinued, but hemorrhagic shock was observed.

Difficulty in diagnosis of PE/DVT related to pregnancy

Many of the typical signs and symptoms of PE/DVT are the same as symptoms of normal pregnancy.[17] The D-

dimer level is not an exclusion criterion for the diagnosis of DVT during pregnancy and postpartum period.[18–20] In addition, there is a risk of CT radiation to the fetus depending on the stage of pregnancy and absorbed dose. The highest radiation risk occurs during organogenesis and early fetal stage before gradually decreasing during the second trimester, with the third trimester having the lowest risk. However, it should be avoided, if possible.[17] No safety of contrast media for fetuses has been established. Therefore, for an imaging study, echosonography of the veins of the lower extremities is the first choice.

Advantage of IVCF

Considering IVCF use in pregnant rather than in non-pregnant patients is necessary because of the difficulty in evaluating symptoms or D-dimer, restrictions on imaging diagnosis, limitations of anticoagulant drugs, difficulty in controlling heparin, and the necessity of stopping anticoagulant therapy at delivery and the tendency for coagulation.

There is no difference in the indication for IVCF during pregnancy or non-pregnancy, and the complication rates are also identical.[21] However, as mentioned above, the treatment of thrombus for pregnant women is more difficult than in normal cases. The inferior vena cava and the iliac veins cannot be clearly observed on echocardiography of the lower extremities because the field in front of the veins is obstructed by the fetus, which makes it difficult to locate any residual thrombus in the pelvis.[22] Additionally, it is commonly thought that thrombi are found only in the pelvis during pregnancy.[23] Because compression of the inferior vena cava is released after delivery, there is a concern about the possible movement of large thromboembolism from the pelvis to the lungs. A randomization study to verify the usefulness of IVCF is ethically challenging, and it is difficult to reliably confirm that IVCF is unnecessary because of the circumstances explained above. Thromboembolism has a major influence on the health of women, and the outcomes of pregnancy can be alarming. There is no certainty that the childbirth will occur as planned, and the period of interruption of anticoagulant therapy might increase because of bleeding. Our study also showed that the interruption period of anticoagulation therapy was long in patients who bled heavily (case 11). Therefore, considering that the highest risk occurs during delivery, it is necessary to consider IVCF use according to each individual case. The rate of thrombus capture of 90.0% in our study is higher than that in previous studies 12.1%–16%,[24,25] anticoagulant therapy interruption may be affected. Among complications, there are reports of venous injury due to the filter and failure to retrieve the filter.[21] In this study, the IVCF (New House Protect) was used. The basket is made from Teflon™, a soft material, which is less likely to damage the vein. It has been reported that 11.25% of filters could not be retrieved.[26] However, this filter is placed continuously outside the body, and hence, is not difficult to retrieve; we have observed 100% retrieval rates at our institution.[27] The filter was inserted suprarenally in all patients because infrarenal insertion was not possible because of the presence of the fetus. Both suprarenal and infrarenal positions are acceptable, although there are more theoretical benefits of suprarenal placement.[21]

Limitations

This was a retrospective study performed in a single institution, and the number of patients was small. A study with a larger number of patients from different institutions is necessary. In addition, adequate anticoagulant therapy was not provided to the patients before subcutaneous self-injection of heparin was approved for reimbursement.

Conclusion

In women diagnosed as having venous thrombosis during pregnancy and treated with anticoagulant therapy and temporary IVCF implantation, there was no maternal or perinatal death and no recurrence of symptomatic PE/DVT.

Disclosure Statement

The authors declare that there are no conflicts of interest.

Author Contributions

Manuscript preparation: TM, TN, TO
Data collection and interpretation: all authors
Critical revision of manuscript: all authors

References

1) Villasanta U. Thromboembolic disease in pregnancy. Am J Obstet Gynecol 1965; **93**: 142-60.
2) Rochat RW, Koonin LM, Atrash HK, et al. Maternal mortality collaborative: maternal mortality in the United States: report from the maternal mortality collaborative. Obstet Gynecol 1988; **72**: 91-7.
3) Syverson CJ, Chavkin W, Atrash HK, et al. Pregnancy related mortality in New York City, 1980 to 1984: causes of death and associated risk factors. Am J Obstet Gynecol 1991; **164**: 603-8.
4) Högberg U, Innala E, Sandström A. Maternal mortality in Sweden, 1980–1988. Obstet Gynecol 1994; **84**: 240-4.
5) Kobayashi T. Blood for perinatal period in obstetrics; pregnancy and thrombosis. Perinat Med 2003; **33**: 192-6. (in Japanese)
6) Heit JA, Kobbervig CE, James AH, et al. Trends in the in-

cidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005; **143**: 697-706.
7) Kobayashi T, Nakabayashi M, Ishikawa M, et al. Pulmonary thromboembolism in obstetrics and gynecology increased by 6.5-fold over the past decade in Japan. Circ J 2008; **72**: 753-6.
8) Kourlaba G, Relakis J, Kontodimas S, et al. A systematic review and meta-analysis of the epidemiology and burden of venous thromboembolism among pregnant women. Int J Gynaecol Obstet 2016; **132**: 4-10.
9) Parunov LA, Soshitova NP, Ovanesov MV, et al. Epidemiology of venous thromboembolism (VTE) associated with pregnancy. Birth Defects Res C Embryo Today 2015; **105**: 167-84.
10) AbuRahma AF, Mullins DA. Endovascular caval interruption in pregnant patients with deep vein thrombosis of the lower extremity. J Vasc Surg 2001; **33**: 375-8.
11) Hayashi M. Medicine group which should be careful on medication for pregnant women. Monthly Pharmaceutical Affairs 2011; **53**: 1085-9. (in Japanese)
12) Nakamura M, Yamada N, Ito M. Novel anticoagulant therapy of venous thromboembolism: current status and future directions. Ann Vasc Dis 2017; **10**: 92-8.
13) McLintock C, Brighton T, Chunilal S, et al. Recommendations for the diagnosis and treatment of deep venous thrombosis and pulmonary embolism in pregnancy and the postpartum period. Aust N Z J Obstet Gynaecol 2012; **52**: 14-22.
14) Takeuchi K. Obstetric medical care manual; for obstetrics abnormality; I obstetrics emergency diseases 7. Pulmonary thromboembolism. Obstet Gynecol 2005; **72**: 1398-404.
15) Miyatani Y, Betsumiya S, Tani A, et al. A case of deep venous thrombosis during the third trimester of pregnancy. Tokushima Red Cross Hospital Medical Journal 2009; **14**: 38-42. (in Japanese)
16) Patterson JA, Roberts CL, Bowen JR, et al. Blood transfusion during pregnancy, birth, and the postnatal period. Obstet Gynecol 2014; **123**: 126-33.
17) Konkle BA. Diagnosis and management of thrombosis in pregnancy. Birth Defects Res 2015; **105**: 185-9.
18) Wang M, Lu S, Li S, et al. Reference intervals of D-dimer during the pregnancy and puerperium period on the STA-R evolution coagulation analyzer. Clin Chim Acta 2013; **425**: 176-80.
19) To MS, Hunt BJ, Nelson-Piercy C. A negative D-dimer does not exclude venous thromboembolism (VTE) in pregnancy. J Obstet Gynaecol 2008; **28**: 222-3.
20) Damodaram M, Kaladindi M, Luckit J, et al. D-dimers as a screening test for venous thromboembolism in pregnancy: is it of any use? J Obstet Gynaecol 2009; **29**: 101-3.
21) Harris SA, Velineni R, Davies AH. Inferior vena cava filters in pregnancy: a systematic review. J Vasc Interv Radiol 2016; **27**: 354-60.e8.
22) Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med 1998; **129**: 1044-9.
23) James AH, Jamison MG, Brancazio LR, et al. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol 2006; **194**: 1311-5.
24) Miyahara T, Miyata T, Shigematsu K, et al. Clinical outcome and complications of temporary inferior vena cava filter placement. J Vasc Surg 2006; **44**: 620-4.
25) Lorch H, Welger D, Wagner V, et al. Current practice of temporary vena cava filter insertion: a multicenter registry. J Vasc Interv Radiol 2000; **11**: 83-8.
26) PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. Circulation 2005; **112**: 416-22.
27) Obayashi T, Niwa A, Miyamoto T, et al. A study on a series of 97 patients with temporary inferior vena cava filter implantation for acute pulmonary embolism. Ther Res 2007; **28**: 1152-5. (in Japanese)