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Pregnancy-related pelvic vein thrombosis

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Abstract

Pregnancy is a hypercoagulable state due to pro-hemostatic changes in the activity of coagulation factors and fibrinolysis and due to progressively increasing pressure on the iliac veins from the growing uterus. Thus, it is not surprising that there is an increased risk for thrombotic events and especially in the pelvic veins. With the trauma of delivery, and particularly caesarian section, the risk is accentuated in the early days postpartum. Multiparity seems to be another risk factor, which may be due to the older age of the patient. The epidemiology, risk factors, diagnosis, management and prognosis of iliac, ovarian and uterine vein thrombosis will be reviewed here, with emphasis on the relation to pregnancy.

Keywords: pregnancy, puerperium, May-Thurner syndrome, ovarian vein thrombosis, uterine vein thrombosis

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Тромбоз вен малого таза, ассоциированный с беременностью

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Резюме

Беременность – это состояние гиперкоагуляции, обусловленное прогемостатическими изменениями активности факторов свертывания и фибринолиза, а также прогрессирующим увеличением давления на подвздошные вены со стороны растущей матки. Таким образом, неудивительно, что существует повышенный риск тромботических событий, особенно в венах малого таза. Риск является повышенным в первые дни после родоразрешения, в частности, после кесарева сечения. Еще одним фактором риска является многоплодие, которое может быть обусловлено более старшим возрастом пациентки. В настоящей работе рассмотрены эпидемиология, факторы риска, диагностика, ведение и прогноз тромбоза подвздошной, яичниковой и маточной вен с фокусом на их связь с беременностью.

Ключевые слова: беременность, послеродовой период, синдром Мэя-Тернера, тромбоз яичниковой вены, тромбоз маточной вены

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Introduction / Введение

The American Obstetrician, Andra James, described in 2005 a cohort of 53 women with pregnancy-associated deep vein thrombosis (DVT), and of those 6 (11) were in pelvic veins [1]. This should be compared with less than 1 % of DVT in the pelvic veins in a registry of over 5,000 patients [2]. Thus, one can approximate that proportionally pelvic vein thrombosis is 10-fold more common in pregnant patient than in other populations. The large pelvic veins are the common iliac, external iliac, and internal iliac veins. Smaller veins include the ovarian,

pudendal, superior and inferior gluteal, and obturator veins as well as the rectal, vaginal, uterine, ovarian and vesical venous plexus. A DVT that progresses from the femoral vein into the iliac vein might often be classified as a DVT of the leg (**Fig. 1**).

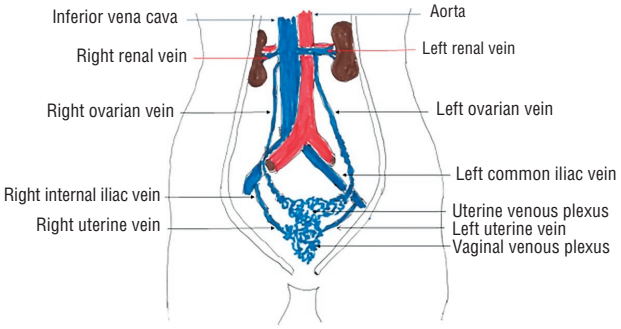

Figure 1. The veins of the female pelvis [drawn by author].

Рисунок 1. Вены женского таза [рисунок автора].

It should first of all be noted that in asymptomatic women with low-risk pregnancy there is a high incidence of thrombosis in the iliac or ovarian veins if they are examined with magnetic resonance imaging (MRI). A study with magnetic resonance venography in 30 such patients after vaginal delivery showed definite evidence of thrombosis in 30 %, probable thrombosis in 27 % and possible thrombus in 10 % [3]. The authors reasoned that this could thus be considered a "normal" finding in this context. Andra James surmised in an accompanying editorial that these thrombi could play a physiological role by reducing bleeding from the placental bed and facilitating involution of uterus [4].

Iliac vein thrombosis and May-Thurner syndrome / Тромбоз подвздошной вены и синдром Мэя-Тернера

Iliac vein thrombosis on the left side is frequently associated with compression of the vein as it is crossed over by the right common iliac artery with the lumbar spine behind. This is the May-Thurner syndrome and thrombosis can develop with or without pregnancy [5]. The pressure on the thin-walled vein and the pulsatile movements of the overlying artery cause intimal hyperplasia in the vein, deposition of collagen that transforms into fibrous tissue and progressively decreased venous flow. Compression of the left iliac vein by more than 50 % was seen on computed tomography (CT) in 12 of 50 (24 %) patients that were examined in the Emergency Room for abdominal pain, none of whom had DVT [6]. Thus, the anatomical variant in itself could be considered as normal rather than pathologic, only resulting in DVT when additional risk factors are present. Scoliosis may aggravate the condition [7], as well as thrombophilic defects (see below) or other hypercoagulable states, including pregnancy.

Clinical presentation / Клиническая картина

In a literature review of 6 studies on patients with May-Thurner syndrome that were treated with endovascular thrombolysis and stenting the population consisted of 72 % females [8]. The symptoms are, in addition to the typical pain and swelling of the leg, also general pain in pelvis or lower abdomen. It should be noted that the iliac vein compression can result in other pathologies than DVT, such as venous insufficiency, venous claudication, lipodermatosclerosis and recurrent superficial thrombophlebitis have been described [9].

Diagnosis / Диагностика

J.Y. Mei et al. reviewed 25 patients with May-Thurner syndrome and undergoing 30 pregnancies at two hospital sites [10]. The syndrome had been diagnosed pre-conception in 14 (56 %) and antepartum in 6 (24 %). Antepartum anticoagulation was prescribed for 96 % of pregnancies in those two subgroups. An inheritable thrombophilic mutation was diagnosed in 11 (44 %) of the patients. The diagnosis in this cohort of patients was achieved in equal proportions with ultrasonography, venography, and MRI. Most patients will initially have ultrasonography, but sometimes the iliac vein is difficult to visualize, due to bowel gases or body habitus. In a study of 181 patients with suspected DVT, the external iliac vein could not be examined in 21 %, whereas for the common iliac vein there was failure in 53 % [11]. More sensitive exams are CT and MRI, but intravascular ultrasound provides the best illustration of the morphology of the venous lesion, the degree of stenosis, and the calibration of the vein prior to insertion of a stent [9].

Therapy / Терапия

Treatment of the DVT in May-Thurner syndrome depends on the duration and severity of the symptoms and the extent of the thrombus. With short duration and extensive thrombus an aggressive approach is often recommended to reduce the risk for severe post-thrombotic syndrome [9]. Surgical thrombectomy has been abandoned and replaced by catheter-directed thrombolysis and subsequent stent insertion. All patients should receive heparin or low-molecular-weight heparin, followed by oral anticoagulation and early mobilization.

Ovarian vein thrombosis / Тромбоз яичниковых вен

The ovarian venous plexus, which communicates with the uterine venous plexus, merges into the right ovarian vein that empties directly into inferior vena cava just below the right renal vein, and into the left ovarian vein that drains into the left renal vein. J.J. Baka et al. described in

2021 • Vol. 15 • № 5
Obstetrics, Gynecology and Reproduction

1989 2 patients with ovarian vein thrombosis and noted that the occluded vein could increase 4-fold in diameter, up to 8 cm, which is probably possible due to the thin adventitia layer [12].

Epidemiology and risk factors / Эпидемиология и факторы риска

In a case-control study from the Mayo Clinic 219 cases with ovarian vein thrombosis were diagnosed. During the same 15-year period 13,417 female cases with DVT in the leg were identified, which is 61-fold more [13]. Over each 5-year period the number of cases with ovarian vein thrombosis diagnosed increased steadily and sharply. Most of the cases had underlying malignancy (44 %) compared to 21 % in a control group with leg DVT, matched for sex and age. However, association with pregnancy showed a trend to higher proportion for ovarian vein thrombosis than for leg DVT – 12 % vs. 7 %, whereas the proportion related to hormonal use was similar in the two groups. Infection was significantly more common for ovarian DVT, whereas trauma was less frequent in comparison with leg DVT. Whereas leg DVT was significantly more common on the left side in this female control group, the women with ovarian vein thrombosis showed a trend to more on the right side. Of 42 patients with ovarian vein thrombosis and tested for thrombophilic defects, only 6 (14 %) had positive results (lupus anticoagulant – 3; factor V Leiden – 2; antithrombin deficiency – 1). In a Canadian retrospective study of 47 patients with ovarian vein thrombosis, 45 cases had information regarding thrombophilia and a defect was known in 4 (9 %) of those (factor V Leiden – 3; protein C deficiency – 1) [14]. More than half of the patients in this study had a concomitant infection, usually endometritis.

The risk of ovarian vein thrombosis in pregnancy has been reported as 0.01 to 0.05 % (**Table 1**). In a study from Parkland Hospital in Texas, including almost 45,000 deliveries, 15 (0.03 %) developed septic ovarian vein thrombophlebitis [15]. A study from Louisiana reviewed more than 60,000 records from deliveries during 1980–1989 and found 30 patients with ovarian vein thrombosis, for an incidence of 0.049 % [16]. In another study of over 40,000 women post-partum during 4 years at Sheba Medical Center in Israel, 13 cases (0.04 %) with ovarian vein thrombosis were identified [17]. The incidence was higher with caesarian delivery (0.1 %) and the highest with caesarian twin delivery (0.67 %). Half of the patients had an infection as additional risk factor. It is thus likely that both trauma to the ovarian veins and local (or remote) infections can induce endothelial injury. Thrombophilic defects were found in 3 (23 %) of the patients (prothrombin G20210A mutation, double heterozygosity for factor V Leiden and prothrombin mutation, and cardiolipin antibodies in 1 each) [17]. Other, pregnancy-specific etiologic factors are the physiological uterine dextrorotation during pregnancy, resulting in compression of the right ovarian vein against the pelvic brim, and length of the right ovarian vein with valve incompetence or lack of valves, and post-partum dilatation of the vein with sluggish flow [18].

Pulmonary embolism was diagnosed in 1 of 26 pregnancy-related in the Mayo Clinic study, 0 of 15 on the Parkland Hospital study, 0 of 13 in the Sheba medical Center study, and 3 of 45 in the Canadian study [13–15, 17], but extension into inferior vena cava occurred in 4, 1 and 9 patients, respectively, among the latter three cohorts, respectively [14, 15, 17].

Clinical presentation / Клиническая картина

The clinical picture, as described by D.R. Dunnihoo et al., adding their 30 cases to 128 from previous literature, is characterized by low abdominal pain on the side of the affected vein in 67 %, fever in 80 %, nausea in 23 %, ileus in 22 % and vomiting in 12 % [16]. They also reported that of the abdominal findings, a palpable abdominal mass (cord-like) was the most typical and present in 46 % of the patients. In addition, there was often tachycardia and fever. Leukocytosis was a common laboratory finding.

A. Rottenstreich et al. reviewed all cases with ovarian vein thrombosis from 5.5 years at three university hospital in Israel and found that the pregnancy-related patients in comparison with non-pregnant women had more often acute symptoms and fever but less often nausea, vomiting and anorexia [19]. The pregnancy-related also had more often leukocytosis and elevation of lactate dehydrogenase. There was a trend to lower prevalence of thrombophilic defects in the pregnant patients (20 % vs. 43 %). They also noted that multiparity was typical, with an average of 3.6 children. The patients presented with symptoms after a mean of 6 days, with a range of 2–37 days after the delivery.

Table 1. Incidence of postpartum ovarian vein thrombosis.

Таблица 1. Частота встречаемости послеродового тромбоза яичниковой вены.

Reference Ссылка	Country, years Страна, годы	Deliveries, n Роды, n	Thrombosis, n (%) Тромбоз, n (%)
Dunnihoo D.R. et al. [16]	USA, 1980–1989	60,585	30 (0.049)
Brown C.E. et al. [15]	USA, 1991–1994	44,922	15 (0.033)
Salomon O. et al. [17]	Israel, 2004–2007	40,353	13 (0.032)
Rottenstreich A. et al. [19]	Israel, 2000–2015	≈ 500,000	60 (0.012)

Diagnosis / Диагностика

Before the availability of ultrasonography, CT and MRI, ovarian vein thrombosis was misdiagnosed as acute appendicitis in 24 % of reported cases [16]. In the Texas cohort from 1991 to 1994 and in the Israeli cohort from 2004 to 2007 CT was used for diagnosis in all patients [15, 17]. For the patients in the Israeli cohort from 2000 to 2015, CT was used in 92 %, ultrasonography in 5 % and MRI in 3 % [19]. A comparative study of 3 diagnostic techniques – transabdominal ultrasonography, CT and MRI – was performed in 76 women with post-partum fever for 5 days and poor response to antibiotics [20]. Twelve women did not complete all 3 techniques, and when at least 2 techniques demonstrated a thrombus it was considered true positive. Likewise, with at least 2 techniques not showing a thrombus it was defined as true negative. Whereas CT and MRI depicted both ovarian veins in all patients, ultrasonography failed to find the right ovarian vein in 48 % and the left in 77 %. Ovarian vein thrombosis was identified in 12 women. The sensitivity and specificity was for MRI 92 % and 100 %, respectively and for CT 100 % and 99 %, respectively. The authors commented that the MR-technique improved during the years of the study (1991–1995) and it has certainly been further enhanced after that.

Management / Тактика ведения

Before 1990 72 % of reported patients with post-partum ovarian vein thrombosis had an invasive procedure as part of their management – ovarian vein excision in 48 %, ligation in 17 % and vena cava ligation in 7 % [16]. Anticoagulation with heparin was given to 83 % and antibiotics to 92 %. The study from Texas in the 1990's included a small randomized trial with 8 patients assigned to antibiotics alone and 6 patients to antibiotics plus heparin [15]. The duration of fever was similar in the two groups and no patient suffered any complications during or after the hospitalization. In the Mayo Clinic cohort (1990–2015) anticoagulation was used in 54 % of the women with ovarian vein thrombosis, typically with transitioning to warfarin and continued for about 3 months [13]. In the more recent cohort from Israel (2000–2015) essentially all patients were anticoagulated (98.6 %), whereas only half received antibiotics [19]. Invasive procedures were not mentioned in these latter studies.

Prognosis / Прогноз

In 1917, C.J. Miller reviewed 182 cases of untreated pelvic pyemia, who did not have ligation or excision of the affected pelvic vein and the mortality was 52 % [21]. C.J. Lenz et al. noted in the Mayo Clinic study that the risk of recurrence, despite the fact that half of the patients were not anticoagulated, was similar to that in a control group with leg DVT (2.3 and 1.8 per 100 patient-years, respectively) during a median follow-up of 1.2 years [13]. One of 26 patients with pregnancy-related ovarian vein thrombosis had a recurrence. In the Israeli study by A. Rottenstreich et al., follow-up was performed with CT (n = 54) or with ultrasonography (n = 20) after a median of 5 months [19]. The thrombus had resolved in all those patients and none of the 60 patients with pregnancy-related ovarian vein thrombosis had a recurrence.

Uterine vein thrombosis / Тромбоз маточных вен

The uterine venous plexus intertwines cranio-laterally with the ovarian venous plexus on each side and eventually draining into the ovarian veins, and caudally with the vaginal venous plexus and then draining into the uterine vein on each side, and those drain into the internal iliac veins. There are hardly any publications on uterine vein thrombosis in pregnancy. Some cases in non-pregnant women with uterine myoma have been reported, and the thrombus can then be misdiagnosed as cystic degeneration of myoma [22].

Uterine vein thrombosis was observed on transvaginal ultrasonography in 39 of 1383 (3 %) non-pregnant women that were examined for a number of other reasons [23]. Independent risk factors for such a finding were family history of venous thromboembolism (odds ratio [OR] = 8.74; 95% confidence interval [CI] = 1.65–46.4), multiparity (OR = 5.75; 95% CI = 2.10–15.7), varicose veins on the legs (OR = 3.15; 95% CI = 1.32–7.49), and recent surgery (OR = 3.10; 95% CI = 1.19–8.07).

The first report on pregnancy-related uterine vein thrombosis is probably one by J.D. Douketis et al. in 1997, describing the case of a 22-year-old female who, after uneventful pregnancy and vaginal delivery, presented with right lower abdominal pain, fever and rigors on the 5th day post-partum [24]. On ultrasonography a round, solid adnexal mass on the right side with surrounding fluid were seen, and when the patient failed to respond to 48 hours of treatment with antibiotics, adnexal torsion was suspected. Therefore, laparotomy was performed and a venous thrombus was found, 3 cm at the widest and between the base of the uterus and the right uterine tube. Treatment was changed to intravenous heparin and the symptoms abated after 48 h.

In 2003 Z. Leibovitz et al. described 4 cases with uterine vein thrombosis detected in the first half of pregnancy [25]. The women did not have any symptoms of thromboembolism. The authors described how the echogenic structures look round (10–16 mm in diameter) on transverse views of transvaginal ultrasonography but are elongated in other views. Color Doppler demonstrated blood flow around the thrombi. Transabdominal ultrasonography failed to identify the thrombi, whereas MRI could support the diagnosis but appeared inferior to transvaginal ultrasonography.

D. Mavrelos et al. published in 2013 a case series with 6 women, diagnosed by transvaginal ultrasonography

2021 • Vol. 15 • № 5
Obstetrics, Gynecology and Reproduction

with uterine vein thrombosis, 2 of which were related to pregnancy [26]. The first of those had early pregnancy loss and the second had ectopic pregnancy, causing compression of the uterine vein with a free-floating thrombus distally.

The patients in these reports were uniformly investigated for thrombophilia, and the results are summarized in **Table 2**. All patients with pregnancy-related uterine vein thrombosis were treated with anticoagulation, initially with heparin/low-molecular-weight heparin and transitioned to warfarin for 3 months [24–26].

Conclusion / Заключение

Pregnancy-related pelvic vein thrombosis includes iliac, ovarian, and uterine vein thrombosis. Iliac vein thrombosis can be isolated or part of a more extensive thrombus in the leg. Left iliac vein thrombosis is often associated with external compression – May-Thurner syndrome, but far from all patients with evidence of compression develop thrombosis. Catheter-directed thrombolysis and subsequent stent insertion is recommended for severe cases. Ovarian vein thrombosis occurs in 0.01–0.05 % of pregnancies, typically post-partum and in at least half of the cases in association with an infection. It can in a small proportion of cases extend into the inferior vena cava and/or cause pulmonary embolism. Diagnosis is preferably established with MRI or CT. The guidelines of the Society of Obstetricians and Gynaecologists of Canada recommends treatment with antibiotics and suggests treatment with anticoagulants. In contemporary cohorts the patients with ovarian vein thrombosis were, however, almost uniformly anticoagulated for about 3 months [27]. Pregnancy-associated uterine vein thrombosis is extremely rare. It is best diagnosed with transvaginal ultrasonography. Management is typically with anticoagulants.

Table 2. Thrombophilia investigations in patients with uterine vein thrombosis.

Таблица 2. Исследования случаев тромбофилии у пациенток с тромбозом маточной вены.

Reference Ссылка	Etiology Этиология	n	Cases with thrombophilia Случаи тромбофилии	Types Типы
Douketis J.D. et al. [24]	Postpartum После родов	1	0	
Leibovitz Z. et al. [25]	Pregnancy Беременные	4	0	
Mavrelos D. et al. [26]*	Pregnancy Беременные Non-pregnant Небеременные	2 4	1 2	aCL аКЛ Protein S deficiency (1), prothrombin gene mutation (1) Дефицит протеина S (1), мутация гена протромбина (1)
Amin T. et al. [23]	Non-pregnant with routine gynecology assessment Небеременные, рутинное гинекологическое обследование	39	5	Protein C deficiency (1), protein S deficiency (1), lupus anticoagulant (1), aCL IgM (1), $a\beta_2$-GP1 IgM (1) Дефицит протеина С (1), дефицит протеина S (1), волчаночный антикоагулянт (1), аКЛ IgM (1), $a\beta_2$-GP1 IgM (1)

Note: *aCL – cardiolipin antibodies; $a\beta_2$-GP1 – β_2-glycoprotein 1 antibodies.*
**Two additional patients were heterozygous for the thermolabile variant of methylene tetrahydrofolate reductase C677T, which is of questionable clinical significance.*

Примечание: *аКЛ – антитела к кардиолипину; $a\beta_2$-GPI – антитела к β_2-гликопротеину 1.*
**Еще две пациентки были гетерозиготными по термолабильному варианту метилентетрагидрофолатредуктазы С677Т, что имеет сомнительное клиническое значение.*

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