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Venous Trhomboembolic Diseases in Gestants Followed at the Centre Médical Diamant in Lubumbashi: Analysis of Diagnosis and Therapeutic Elements

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Abstract: Pregnancy is one of the main risk factors for the development of venous thromboembolic disease (VTED). The objective of this work was to analyze the diagnostic and therapeutic elements of venous thrombosis in pregnant women followed at the Centre médical Diamant in Lubumbashi (CMDL). This is a descriptive cross-sectional study over a period of 27 months at CMDL in DR Congo, including all pregnant women followed for venous thrombosis during the study period. Data analysis was done by SPSS 22.0 software. The prevalence of VTED was 5.2% with a mean age of 27 ± 3 years (Extreme: 21 to 42 years). The telltale signs were dominated by asymmetric swelling of the lower limb (27.3%) and the main location was femoro-popliteal (63.6%). Superficial venous thrombosis was predominant with 54.5%. The diagnosis of VTE was supported by measurement of D-dimer in 100% of cases, confirmed by Doppler ultrasound in 81.8% of cases. Associated factors were non-O blood group (45.5%), history of miscarriages (27.3%), family history (18.2%), age over 35 years (18.2%), multiparity (27.3%) and gestational diabetes (18.2%). The treatment combined low molecular weight heparin in 72.7%. The mean duration of treatment was 28 days (range: 18-42 days). The outcome was favorable in 63.6% of cases. Venous thrombosis in pregnancy remains a major challenge in our environment because the risk factors and specific determinants are not known, there is no preventive or curative protocol adapted to our working conditions. Further, more in-depth studies are needed to optimize and rationalize care.

Keywords: Pregnancy, Venous Thrombosis, DR Congo

1. Introduction

The prevalence of venous thromboembolism (VTE) in France during pregnancy is of the order of 0.5 to 2 per 1000 pregnancies [1]. It is responsible for major maternal morbidity and mortality since it is the third leading cause of maternal mortality in the West, after postpartum hemorrhages and amniotic embolisms. [2]. Pulmonary embolism (PE) alone accounts for five to ten deaths per year in France and the United Kingdom [3], of which a third would be preventable since they are mainly correlated with diagnostic and therapeutic delays. Pregnancy alone (due to the change in

hemostasis) is responsible for a six to fifteen times greater risk of VTE than in a woman of the same age who is not pregnant and not taking estrogen-progestogen therapy. [2-5]. These thromboembolic events can occur throughout the three trimesters of pregnancy and are in 85% of cases, Deep Vein Thrombosis (DVT). On the other hand, during the postpartum period, it is PE that occurs in 60% of cases. However, since the postpartum period is shorter than pregnancy, the risk of developing VTE is, therefore, three to fifteen times higher in the postnatal period. These figures therefore explain the establishment of a prevention policy for VTE, both primary, by identifying risk factors for VTE, and secondary, by the implementation of prophylactic or curative treatment (depending on the risk factors found) early [5, 6].

It is important to note that VTE is a multifactorial disease. Several clinical and obstetric risk factors are reported much more in the Western literature. However, some reviews contradict each other on the level of evidence for these factors. Indeed, if some studies have been carried out during pregnancy, most have been carried out in non-pregnant women, then extrapolated in pregnant women in particular: an age greater than 35 years, with a risk in the antenatal period multiplied by two for patients. DVT and by three for PE, A body mass index (BMI) greater than 25 kg/m^2, heavy smoking (greater than 10 cigarettes per day), multiparity greater than two or three, multiple pregnancy, cesarean section, especially when it is performed urgently (risk in the postnatal period), a personal history of VTE, family history of VTE, medically assisted procreation (AMP), prolonged bed rest, African or Asian ethnicity, non-O blood group, certain obstetric pathologies (pre-eclampsia, eclampsia, intrauterine growth retardation, retroplacental hematoma and fetal death in utero), postpartum hemorrhages, gestational diabetes, Systemic lupus erythematosus, inflammatory diseases, the presence of significant varicose veins, instrumental maneuvers, hereditary or acquired biological risk factors. [6, 7]

Faced with clinical warning signs, the confirmatory diagnosis is both biological and ultrasonic. Very often these examinations are expensive or even impractical in countries with limited resources, thus limiting the field of investigation even in the face of certain signs of anamnestic or physical calls [5, 8]. This explains all the difficulty in obtaining reliable statistics in our environment, and if we are to believe it, we risk thinking that our pregnant women are spared, with a high probability of diagnosing them in the complications phase, in particular unforeseeable, brutal and fatal pulmonary embolisms, especially in our structures which are still under-equipped.

It is the same for the management grouping together several protocols according to the schools, but this reality is difficult to apply in our environment given that we do not control the risk factors and determinants specific to our environment.

Studies demonstrating the performance of diagnostic algorithms for suspected DVT or PE have excluded pregnant women. The safety of a simple extrapolation of the data to this collective therefore remains to be confirmed [9, 10, 11]. In addition, the clinician is then faced with a real dilemma: on the one hand, the fear of a missed diagnosis of VTE, the outcome of which can be fatal, and, on the other hand, the reluctance to carry out additional broad examinations. Scale, in particular in the case of PE, because of the risks associated with irradiation for the fetus but also for the mother.

In order to improve the early diagnosis as well as the overall management of venous thrombosis in obstetrics in our environment, in Lubumbashi, the objective of this work is to analyze the different forms of VDM and their management.

2. Patients and Methods

This was a preliminary descriptive and cross-sectional study focusing on the analysis of the diagnostic elements and the management of venous thrombosis in pregnant women in our environment over a period of 27 months (November 2018 to February 2021). This work was carried out at the CMDL, chosen as the pilot center, given its great capacity to accommodate pregnant women, its obstetrical technical platform, and its academic partnership vocation. Were included, all pregnant women having presented some risk factors for thromboembolic disease described in the literature and/or those presenting characteristic symptoms and whose files could be used with a previously signed informed consent. Those not meeting these conditions were not included in our study. Our sampling was exhaustive targeting a minimum size allowing just to highlight the key elements of the managerial problem of these patients in our environment. The explanatory variables were socio-demographic, clinical, paraclinical, therapeutic and evolutionary explaining the occurrence of venous thrombosis in pregnant women in our environment. Among the examinations, the measurement of D-dimers was carried out on the ichroma apparatus according to the Elfa technique (Enzyme Linked Fluorescent Assay), the exclusion threshold for MTEV being set at 500 ng/mL. In a documentary review, Nougier and Marijon (2012) [11] indicate that in normal individuals, D-dimer levels vary to a certain extent depending on age but they remain below 500 ng/mL up to 50 years while in healthy pregnant women, they vary greatly with an average of 227 + 79 ng/mL in the 1st trimester), 735 + 552 ng/mL in the second trimester and 1176 + 905 ng/mL in the third trimester of the pregnancy. In the present work, we consider as pathological, any value of D-dimer greater than 500 ng/mL in the 1st trimester of pregnancy, 1000 ng/mL in the second trimester and 2000 ng/mL in the third trimester and in the postpartum. Doppler ultrasound on the Chison Q9 brand device with color display. The data was first encoded in Excel software for analysis by SPSS 22.0 software. The principles of confidentiality were respected and informed consent was obtained beforehand.

3. Results

In pregnant women with venous thrombotic diseases

during the study period, the prevalence was 5.2% (11 cases out of 213 deliveries performed during the period) and the mean age was 27 ± 3 years with extremes ranging from 21 at 42 years old. The majority of thromboses (45.5%) were diagnosed in the second trimester of pregnancy (Table 1).

Table 1. *Distribution of pregnant women with venous thrombosis according to gestational period.*

Period	Effective	Percentage
First Trimester	2	18.2
Second trimester	5	45.5
Third Trimester	3	27.3
Post partum	1	0.9

The main associated factors were, blood group not O (45.5%), history of miscarriages (27.3%), family history (18.2%) as well as age over 35 years (18/2%). (Table 2).

Some of the main factors associated with pregnancy and childbirth were:

1) Multiparity (27.3%) and Gestational Diabetes (18.2%).
2) Emergency cesarean section 1 case (0.9%) and spontaneous vaginal delivery 2 cases (18.2%).
3) Clinical warning signs: the main revealing signs were: asymmetric swelling of the lower limb 3 cases (27.3%), heaviness of the limb 2 cases (18.2%), varicose veins 2 cases (18.2%), Dyspnoea + hemoptysis 1 cases (0.9%) and asymptomatic 3 cases (27.3%).(Table 3).

Table 2. *Distribution of pregnant women according to the main risk factors before pregnancy.*

Socio-demographic factor	Effective	Percentage
Age over 35	2	18.2
Non- O blood group	5	45.5
BMI greater than 25 Kg/m^2	3	27.3
Personal history	1	0.9
Family history	2	18.2
Venous insufficiency	1	0.9
History of miscarriages	3	27.3

Table 3. *Distribution of patients according to risk factors associated with pregnancy.*

Risk factors	Effective	Percentage
Multiparity	3	27.3
Placental vascular pathology	1	0.9
Third trimester bleeding	1	0.9
Gestational diabetes	2	18.2
Pre-eclampsia	1	0.9
Immobilization	1	0.9

The main locations were: femoro-popliteal (63.6%), anterior tibial (18.2%) and external iliac (18.2%). Superficial venous thrombosis was predominant (54.5%), followed by deep thrombosis (36.4%) and 1 case (0.9%) of pulmonary embolism in the context of postpartum COVID-19.

It emerges from Table 4 that among the paraclinical elements supporting the diagnosis of VTE, D-dimers, blood platelets, the level of prothrombin and the activated partial thromboplastin time were systematically carried out in pregnant women with signs of venous thrombosis.

Table 4. *Distribution of pregnant women according to the paraclinical examinations carried out.*

Exams	Effective	Percentage
D-Dimers	11	100
Doppler ultrasound	9	81.8
Fibrinogen	4	36.4
Platelets	11	100
Prothrombin	11	100
Activated Cephalin Time	11	100
International Normalized Ratio (INR)	9	81.8

The D-dimers were pathological in all 11 cases, with values ranging from 2900 to 10,000 ng/mL and this taking into account the values of D-dimers depending on the patient's age and due to the presence of pregnancy, either beyond 500ng/mL in 2 cases in the first trimester, beyond 1000ng/mL in 5 cases in the second trimester and beyond 2000ng/mL in the third and postpartum period in 4 cases. Doppler ultrasound confirmed VTE in 9 cases.

Among the selected biological risk factors, we mainly had protein S deficiency in 2 cases (18.2%), protein C deficiency in 2 cases (18.5%), low INR in 5 cases (45.5%), thrombophilia in 3 cases (27.3%), High Prothrombin level 2 cases (18.5%).

For prevention, no patient had received any preventive treatment despite the risk factors observed.

In curative treatment, the different protocols combined low molecular weight heparin only 8 cases (72.7%), low molecular weight heparin + Anti vitamin K1 2 cases (18.2%), Non-Fractionated heparin 1 case (0.9%). As adjuvants, were used compression stockings 6 cases (54.5%), venotonics 7 cases (63.6%), and antiplatelet aggregates 2 cases (18.2%).

The follow-up of pregnant women had been mainly supported by the dosage of D-dimers, platelets, INR and the performance of ultrasound without a well-defined chronogram.

The average duration of treatment was 4 weeks with extremes ranging from 18 days to 6 weeks. The outcome was favorable in 7 patients and unfavorable in 4 patients, including 2 cases of persistence and 2 cases of discontinuation of treatment for persistent bleeding. We also report one case of recurrence among the 7 cases declared to be cured.

4. Discussion

Prevalence: our study shows a prevalence of 5.2% of venous thrombosis over a period of 27 months. This prevalence appears to be high given that in the West it is still below 3% [1]. In Africa, some studies had found a predominance of obstetric factors in the occurrence of venous thrombosis [2, 3], which proves that the prevalence must be high there, especially since the black race is also an important risk factor [3, 4].

Risk factors: In our study, we mainly found several factors associated with VTE: age and non-O blood group,

overweight, history of miscarriages. In the literature, these different factors are associated with a modestly increased increase in VTE. Indeed, Jacobson [12], Kane [13] or even Simpson [14] have all three demonstrated the effect of age on venous thromboembolic complications in the antenatal period, by conducting large-scale studies, respectively in Norway, in Scotland and London, bringing together between 365 and 615 cases of VTE during pregnancy. In addition, Simpson [14] also demonstrated the role of blood groups A, B and AB in the risk of occurrence of venous thromboembolic episodes (TEE), risk slightly increasing with an odds ratio between 1.6 [0.9 - 2.9], and 1.9 [1.2 - 3.0].

Period of onset: our study shows that the majority of cases of thrombosis were diagnosed. Overall, the incidence of VTE appears to be higher in the pre-partum than in the post-partum period [15]. Several studies are inconsistent with the incidence of VDTs during pregnancy. Indeed, according to the study conducted by Gherman [16] involving 165 patients, 74.8% of venous TEEs occurred during pregnancy with almost half (49.5%) detected before 15 WA. He therefore noted that the risk of thromboembolism has a higher incidence in early pregnancy. In addition, other studies indicate a homogeneous distribution of venous ETA during the three trimesters of pregnancy. This is the case for Witlin [17, 18] who carried out his study concerning VTE in 1999, on a single hospital center. The 38 patients in its population presented their TEE homogeneously during the three trimesters of pregnancy. In our study, the number appears to be homogeneous between the three trimesters of pregnancy or even post partum.

Forms of venous thrombosis: Our study shows that superficial venous thrombosis was predominant (54.5%), followed by deep thrombosis (36.4%) and 1 case (0.9%) of pulmonary embolism in a context of COVID-19 in post partum. In 2006, a meta-analysis carried out by James et al. [18] had shown that two-thirds of DVT cases occurred in the antenatal period and 60% of PE occurred in the postpartum period, as did DVT complicated with PE which mostly developed after childbirth. These observations were also made in a work carried out over a period of eight years, including 13455 women in the RIETE registry [19] (which is an international study that studied a prospective cohort of patients hospitalized for an ETA). Among pregnant women, 78.0% had had DVT, 13.9% had PE, and 8.1% had complicated DVT of PE. Among postpartum women, 61.0% reported DVT, 23.4% single PE, and 15.6% DVT and associated PE. It was therefore concluded that DVT mainly occurred during pregnancy unlike PE which are most of the time detected during the postpartum period. The small size of our sample could explain certain fluctuations.

Prophylactic treatment initiated: in all pregnant women, no prophylactic treatment was given despite the presence of numerous contributing factors. In addition, there are no studies that have evaluated the effectiveness of heparins as part of prophylactic treatment for VTE in obstetrics [17]. Some studies, such as that in Canada [19], have shown comparable efficacy between LMWH and UFH for prophylaxis in patients with risk factors for VTE other than pregnancy. This prophylaxis remains a great avenue to be exploited, especially in Africa if certain predictive factors are well targeted in relation to a given environment.

Decisive diagnostic elements: It emerges from this work that D-dimer and ultrasound had mainly served as gold standard for the diagnosis of venous thrombosis in our pregnant women. Indeed, the D-dimer assay is used to exclude the diagnosis of VTE, because of its high sensitivity and therefore its high negative predictive value. D-dimers increase steadily during pregnancy. Although charts could be performed, the diagnostic value of an assay whose threshold of negativity would be modified according to the trimester of pregnancy has not been evaluated. Although the likelihood of having a negative D-dimer result in other words, the clinical usefulness of the test decreases as the pregnancy progresses. At the usual test threshold, the exclusion performance is a priori maintained. D-dimers are of particular interest because, if they are negative in a woman with a low clinical probability of PE, radiation tests can be avoided. On the other hand, we recently validated its use in pregnant women by a pragmatic study with follow-up, in which the risk of thromboembolism at 3 months was low in the group of women where the diagnosis of DVT had been ruled out on the basis of 'a complete negative Doppler ultrasound [21]. However the current international recommendations are to repeat the examination when it is negative.

Therapeutic protocol and evolution: the anticoagulant protocol using low molecular weight heparin (LMWH) regardless of the age of pregnancy was the most used, although with other combinations with anti-vitamin K1 or heparin Not Fractionated. Currently, there is evidence that LMWHs have been widely used in pregnant women with satisfactory safety for both mother and child. They do not have a marketing authorization (MA) in several countries for the curative treatment of VTE during pregnancy, but they are however widely recommended and preferred to unfractionated heparin (UFH) by medical professionals, professional consensus and by national and international learned societies [22, 23].

High-risk patients should receive LMWH prophylaxis during pregnancy and postpartum (for 6 weeks) [24]. This duration was not well respected in our series as it was on average 4 weeks with a lower extreme of 18 days. This could be explained by the fact that there is no standard protocol validated in our environment, each practitioner being encouraged to randomly plan this duration. In addition, some patients had stopped treatment for lack of financial means or because of certain side effects, in particular bleeding.

5. Conclusion

The preliminary results of this descriptive study on the diagnostic and therapeutic issue of venous thrombosis in Lubumbashi show that VTE is a public health problem in obstetrics due to its prevalence, the absence of determinants and risk factors specific to our environment, l 'absence of a

preventive and curative protocol or even of follow-up procedures. Other more in-depth studies with a large sample size are recommended in order to develop a predictive score based on determinants specific to our environment as well as to experiment with a curative and preventive protocol adapted to the realities on the ground.

Authors Contributions

We attest that all the above-mentioned authors contributed as much in the design, the methodology, the collection and the treatment of the data, as well as the final correction.

Conflicts of Interest

All the authors do not have any possible conflicts of interest.

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