Review Article

THE NON PHARMACOLOGICAL 3: AN IN-DEPTH REVIEW AND RECOMMENDATIONS FOR VENOUS THROMBOEMBOLISM PREVENTION IN THE PERIPARTUM PERIOD IN LOW AND MIDDLE INCOME COUNTRIES

ABSTRACT

Venous thromboembolism is a significant direct cause of maternal mortality worldwide. Most women who suffer from venous thromboembolism have identifiable risk factors and therefore it is considered a largely preventable condition. There are 2 main ways of preventing this, pharmacological and non-pharmacological. The main pharmacological means of preventing venous thromboembolism include the use of low molecular weight heparin. This is an expensive method and it is sometimes not available in most parts of low and middle income countries due to economic push and pull factors. Even when it is available, majority of the women are unable to afford it, and those who can, get inadequate treatment in form of inappropriate dose or duration of treatment. We shed light on the 3 non-pharmacological methods of prevention of venous thromboembolism and provide recommendations on how it can be deployed in the peripartum period in low and middle income countries to maximise its potential benefit.

Key Words: venous thromboembolism, non pharmacological

1. INTRODUCTION

Everyday, almost 800 women die from maternal mortality. Although maternal mortality ratio has decreased by almost 34% from 2000 to 2020, it is still unacceptably high. 95% of these deaths occur in low and middle income countries and most of these deaths are preventable. The commonest causes are haemorrhage, infection, hypertensive disease in pregnancy and unsafe abortion.

Venous thromboembolism remains one of the highest direct causes of maternal mortality and causes 3% of the all maternal deaths worldwide[1,2].
Venous thromboembolism (VTE) is the formation of a blood clot in a vein which affects adults of all ages and ethnicities. This can be subdivided into 2 main types. Clots occurring in the deep veins are called deep vein thrombosis (DVT), and those occurring in the lung and heart circulation are known as pulmonary embolism(PE)[30].

VTE is considered largely preventable, as most of the women who suffer from it during pregnancy have identifiable risk factors that can easily be picked up. Prevention of VTE can be pharmacological and non-pharmacological but it is often a mixture of both. The non-pharmacological methods include the use of compression stockings, hydration and early mobilisation. Properly utilised, it could prove useful in the fight against maternal mortality associated with thromboembolism, either alone or as an adjunct to the pharmacological methods especially in low and middle income countries. For women who are at high risk of bleeding- as occurs in a significant proportion of pregnant women or who have a contra-indication to receiving the pharmacological method, the non-pharmacological methods can be the mainstay of thromboprophylaxis.

2. BACKGROUND

VTE occurs because of interactions between 3 main factors which is popularly called the Virchow's triad. This classic triad includes venous stasis , endothelial damage and hyper-coagulability[4]. Pregnancy is an independent risk factor for VTE, increasing the relative risk of VTE by 4-6 fold antenatally, and 25-84 fold in the postpartum period, above the non pregnant, non postpartum state[5,6,7]

Pregnancy induces a prothrombotic state. This starts at the beginning of pregnancy, causing an increasing in coagulation factors such as factor I,VII, VIII, X and XII and a decrease in anticoagulants such as protein S and acquired resistance to activated protein C. Impairment of fibrinolysis, mediated by plasminogen activator inhibitor also plays a crucial role[8].

With the hormonal changes that occur in pregnancy- most notably an increase in progesterone, oestrogen and relaxin, there is systemic vasodilation and increased venous capacity due to dilated vessels. This decreases blood flow and leads to a hemodynamic state that favours less circulation of blood and more stasis. The enlarging gravid uterus also contributes to this risk of thrombosis by contributing to venous stasis through impairment of venous return from the lower limbs[9]. Pregnant women are less mobile especially as pregnancy advances and this could increase their overall risk.

Pregnancy associated risk factors for VTE include caesarean section, pre-eclampsia, obstetric haemorrhage, preterm delivery and postpartum haemorrhage. Age, Increased BMI and medical conditions like SLE and IBD could increase the risk of venous thromboembolism in pregnancy[10,11].
Though the use of low molecular weight heparin is a very effective means of preventing VTE, it is not widely available largely due to economic factors. Low molecular weight heparin mostly acts on the hyper coagulable component of the Virchow's triad whiles the non pharmacological methods acts on the stasis and endothelial damage component of the Virchow's triad. Used correctly, they can be an effective method of prevention of venous thromboembolism.

3. REVIEW AND RECOMMENDATIONS

3.1 TED STOCKINGS

Thromboembolic Deterrent(TED) stockings, also known as compression stockings or anti-embolism stockings were first developed by Conrad Jobst [12] around 1950 to treat chronic venous insufficiency. Since then, there has been numerous adaptations to redevelop it further and make it more suitable for use in the current world-the two main types being graduated compression stockings and intermittent pneumatic compression.

The graduated compression stockings are made of elastomeric yarns, capable of recoiling back to their original size and shape after being stretched[13].

They exert graded circumferential pressure distally to proximally(14)and when combined with muscular activity, provide pressure over the superficial veins, muscles and arteries of the lower limb. By doing this, they reduce the diameter of the superficial vessels and this forces blood through the superficial veins to the deep veins and keeps blood moving, thereby preventing stasis[15]. They are capable of increasing blood flow by as much as 138% above the baseline velocity [16].

All the 3 components of Virchow's triad has been found to increase in pregnancy, and stasis being one of these components, is eliminated by compression stockings, thereby reducing the risk of thrombosis in the deep veins significantly. They have also been found to address the vessel wall damage that can contribute to thrombosis formation[17].

There are no clinical trials to support the use of anti-embolic stockings in pregnancy and puerperium and most recommendations are derived from studies done in non-pregnant hospitalised patients. The evidence for their efficacy in these groups of patients is clear and undeniable. In a large Cochrane review, Graduated Compression Stockings were found to be effective in prevention of VTE in hospitalised patients[18]. Extrapolations can therefore be made for pregnant women as the mechanism of action by which they work in pregnancy and puerperium is the same as in non-pregnant women.

The most common cause of VTE in pregnancy is the deep vein thrombosis and majority occur in the iliofemoral vein especially of the left lower limb[19]. Most retrospective cohort studies have found the first 3 weeks postpartum to be the period with the highest incidence of VTE- with some showing highest incidence in the first week whiles others showed highest incidence in the second week. This incidence then decreases over the 3-6 week period postpartum[5,19,20,21,22].

There is little data on the most effective length of compression stocking to use in pregnancy. Data from papers in non pregnant population suggest that there is no difference in the effectiveness of either thigh length or knee length compression stockings[23,24,25,26]. However in these populations, the commonest site of VTE is the calf veins as compared to the ilii-femoral veins in pregnant women. Knee length compression stockings have the advantage of being cheaper, having less complications and being easier to wear, which is an advantage in the pregnant population as it aids compliance[23,26].

Based on these available evidence, the writers recommend the following:

Women wear compression stockings when they are admitted for delivery.

Knee length compression stockings is advocated for because of the advantage of cost, compliance and having less complications.

Women classed as low risk can stop wearing them once discharged, but those classed as medium or high risk should be encouraged to wear them for at least 2 weeks postpartum with the aim for 3 weeks if very high risk.

3.2 HYDRATION

Hydration is one of the non-pharmacological steps in the prevention of venous thromboembolism. It is crucial in the prevention of VTE in both surgical and medical patients. In low and middle income countries, VTE prevention with hydration should not have any economic consequences compared to the the pharmacological method of VTE prevention. Hydration counteracts dehydration, which increases risk of VTE.

The effect of dehydration on the coagulation system was evaluated in a mouse model, showing a significant increase in the tendency to form clots in the dehydration state[27]. Dehydration results in reduced water content in the blood, leading to increased viscosity. Dehydration can also cause electrolyte imbalance which can have effect on the integrity of blood vessels resulting in pooling of blood and subsequent clot formation.

Dehydration also leads to haemo-concentration, resulting in reduction of circulating blood volume, which can lead to vascular stasis. Stasis is one of the primary components of Virchow's triad.

Dehydration reduces total plasma volume, decreases cardiac output, reduces blood flow to muscle, and can change blood rheology, resulting in an an increase in local hematocrit and blood viscosity[28].

Although it is widely assumed that dehydration predisposes to VTE, there are no clinical studies to support this(29) However, expert advisory committees and international guidelines have highlighted dehydration as a risk factor.

Pregnant women are predisposed to dehydration especially in the peripartum period. For those undergoing vaginal delivery, the labour process is an energy consuming task that can leave the women very dehydrated. Also, the various hormonal changes and medications that are given during this period induce nausea and vomiting and puts the woman at risk of dehydration. The sheer presence of pain can also reduce appetite for oral intake[30,31].

Women who are undergoing caesarean sections are also at risk of dehydration. For elective caesarean sections, there could be a delay in the the start time of cases and this could lead to dehydration especially for cases that are done later in the day. Medications given(anaesthesia drugs and antibiotics) could lead to vomiting and pre-dispose the woman to further dehydration. Blood loss at delivery is also a major contributor.

In low resource countries, vitals and physical examinations of patient can help in the assessment of the hydration state of the patient. Some laboratory findings can also play an important role in estimating the hydration status.Dehydration generally causes BUN (Blood Urea Nitrogen) levels to rise more than the creatinine levels, which causes a high BUN-to-creatinine ratio. In some studies, a high BUN-to-creatinine ratio is an indicator of dehydration. High urine specific gravity test indicate a substantial loss of fluid. Measuring blood and/or urine osmolality is also strong indicator of dehydration[32].

Although several clinical and laboratory tests have been applied for accurate diagnosis of dehydration severity, there is no definite absolute cutoff value. Weight loss, skin turgor, deep breathing, and capillary refill time have some limitations because baseline levels were not evaluated[33,34]. Urea concentration ≥100 mg/dL, bicarbonate level ≥15 mEq/L, and serum osmolality have also been used for the diagnosis of dehydration severity[35,36].

Recently, several studies have shown that BUN/Cr ratio >15 is a reference marker for early neurological deterioration[37,38]. A study carried out indicated that BUN/Cr ratio >15 is highly associated with VTE in AIS (Acute Ischaemic Stroke)[34,39].

Also, given the association between VTE and dehydration after AIS, the findings suggest that encouraging fluid replacement may also reduce the likelihood of developing VTE especially in dehydrated patients with AIS presenting with BUN/Cr ratio >15[40].

Hydration of patients can be in the form oral or enteral and parenteral. Given that most obstetric patients are healthy enteral route will be the preferred means of hydration.

Based on the available evidence the writers recommend:

For labouring women, a close monitoring of their intake and output should done throughout the active phase of labour. Women who do no take in appropriate amount of fluids based on the judgement of the carer should undergo a clinical assessment of dehydration and be put on an input and output chart to determine their fluid balance and correct any dehydration that may be present.

Women undergoing a planned caesarean section will usually be told not to eat again after their last meal the night before. Proper prioritisation of the caesarean section list should then be done. Where it is anticipated that there will be a delay in the start time of a case(generally > 6 hours) or where a case has been deemed low priority and hence likely to commence later, the patient should be encouraged to drink and take a light meal in the morning to prevent significant dehydration.

Women who underwent any planned or emergency procedure in theatre should continue iv fluids post-delivery especially if they had some sort of regional or general anaesthesia. Oral intake should be encouraged in the immediate postpartum period for those who have no contraindications to oral intake, as soon as they are able. For women who are unable to tolerate oral intake, maintenance intravenous fluids should be continued till they are able to fully tolerate oral fluids.

After the early postpartum period, women who are deemed to be high risk of VTE should be encouraged to drink more than they would and not necessarily to thirst (as this akin to allowing dehydration to occur and correcting it) especially in the first 3 weeks of pregnancy. Having a means of monitoring their input like taking note of the number of glasses they have drank in a day could help them know if they are taking in enough or not.

3.3EARLY MOBILISATION

Immobilisation has been described as a major risk factor for VTE[41]. Studies have described a risk as high as 8 fold, for developing VTE in patients confined to bedrest whether in hospital or outside of hospital [42].In young and middle aged individuals (as most pregnant women are), immobility is an established risk factor for thrombosis [43].

Prolonged bed rest or immobilisation leads to peripheral muscular and diaphragmatic dysfunction which then contributes to venous stasis[44], inflammation and hyper-coagulability[45].

This is evident during labour and delivery because most women hardly ambulate during such periods. Also, in some low and middle income countries, certain cultural beliefs demand women to be in bed with their babies for days to weeks after delivery, while receiving congratulatory greetings from family and friends.

Additionally, the widespread use of epidural analgesia, howbeit in more developed countries, increases likelihood of immobility in the intrapartum period and hence VTE. With the increased rate of caesarean delivery worldwide, more and more women are prone to being immobile due to regional anaesthesia usage prior to caesarean delivery. All these predispose them to VTE because of minimal or no mobilisation at all in the intrapartum and postpartum

It is therefore essential to encourage early ambulation and to mobilise patients as quickly as possible[46]. Early mobilisation, within 24 h, is an essential component of ERAS protocol as well as a prognostic factor[47] and it is strongly recommended [48] as part of a multidisciplinary approach that involves anaesthesiologist, surgeon, physiotherapist and the nursing team.

Besides its positive impact on the resumption of gastrointestinal transit and tolerance of feeding, it reduces the incidence of post-operative thromboembolic and medical complications [49].
In the MEDENOX study [50] Amin et al. have shown that an active ambulatory status reduces the risk of VTE significantly, especially when it is associated with thromboprophylaxis[51,52].

Based on the following evidence, the writers recommend the following:

Encouraging mobilisation during labour- both in latent and active phase. The use of devices such as the birthing balls encourages physical activity together with helping with labour mechanism.

Even when epidural is being used, patients should be aided to change positions regularly with the help of their carers.

Only using urethral catheterisation when absolutely necessary, i.e. to monitor urine output in cases of high suspicion of going to theatre or suspected or diagnosed kidney failure. Established protocols should be developed that encourage early removal of urethral catheter.

Adequate pain management during labour and postpartum, especially after a caesarean section. Women have different thresholds for pain and listening to women with regards to their pain control goes a long way to help them mobilise.

For elective caesarean sections, practices that encourage women to mobilise, if stable, such as walking to the theatre sets a precedents post delivery.

Other activities that improve the overall muscle activity and health, such as deep breathing exercises, which helps diaphragmatic excursion and free movement of blood, and making use of physiotherapy for in-bed mobilisation exercises for women who struggle to mobilise early.

4. CONCLUSION

In conclusion, we have elaborated on the 3 main non pharmacological methods of VTE prophylaxis in the intrapartum and postpartum period. In low and middle income countries where low molecular weight heparin may not be used to the same standard worldwide non standardised practice, getting the maximum benefit from the non pharmacological methods can prove pivotal in the fight against maternal morbidity and mortality related to VTE.

COMPETING INTERESTS
Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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Option 1:
Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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ABBREVIATIONS

VTE- Venous Thromboembolism