Keywords Haemodilution/Anaemias/Preeclampsia/Thromboembolism

This article has been double-blind peer reviewed

In this article...

- How blood volume and composition changes may link to physiological and pathological anaemias
- Links between cardiovascular and blood pressure changes, and the potential for preeclampsia
- The potential for activating Virchow's triad and increased risk of venous thromboembolic events

Pregnancy 1: effects on haematological and cardiovascular systems

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Key points

Blood volume increases by around 48% during pregnancy

Physiological and pathological anaemias are common

The heart increases in size and is shifted slightly upwards

Blood pressure normally decreases in the first and second trimesters

Risk of deep vein thrombosis, pulmonary embolism and stroke increases

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Abstract Pregnancy is associated with an increase in blood volume of around 48% leading to haemodilution and physiological anaemia. The heart is displaced upwards, the myocardium thickens and cardiac output increases. Progesterone and oestrogen stimulate vasodilation to accommodate increased blood volume leading to a drop in blood pressure in the first and second trimesters. Around 3-5% of pregnancies worldwide are associated with hypertension indicative of preeclampsia. The extra strain placed on the cardiovascular system during a normal pregnancy may reveal underlying cardiac disease for the first time. Pregnancy is associated with a hypercoagulable state and may activate Virchow's triad, increasing the risk of venous thromboembolic events.

Citation Knight J (2023) Pregnancy 1: effects on haematological and cardiovascular systems. *Nursing Times* [online]; 119: 9.

Pregnancy is associated with major changes to maternal physiology with virtually all organs and organ systems adapting to provide an optimal environment for a successful gestation and delivery. This series of articles will explore the anatomical and physiological changes that occur during pregnancy and highlight some of the common complications associated with these changes.

This first article in the series will focus on changes to blood volume and composition and associated changes to the cardiovascular system. These two areas are known to undergo particularly dramatic changes during the nine months of pregnancy; these will impact upon the physiology of many other organ systems since virtually all areas of the human body have a circulating blood supply.

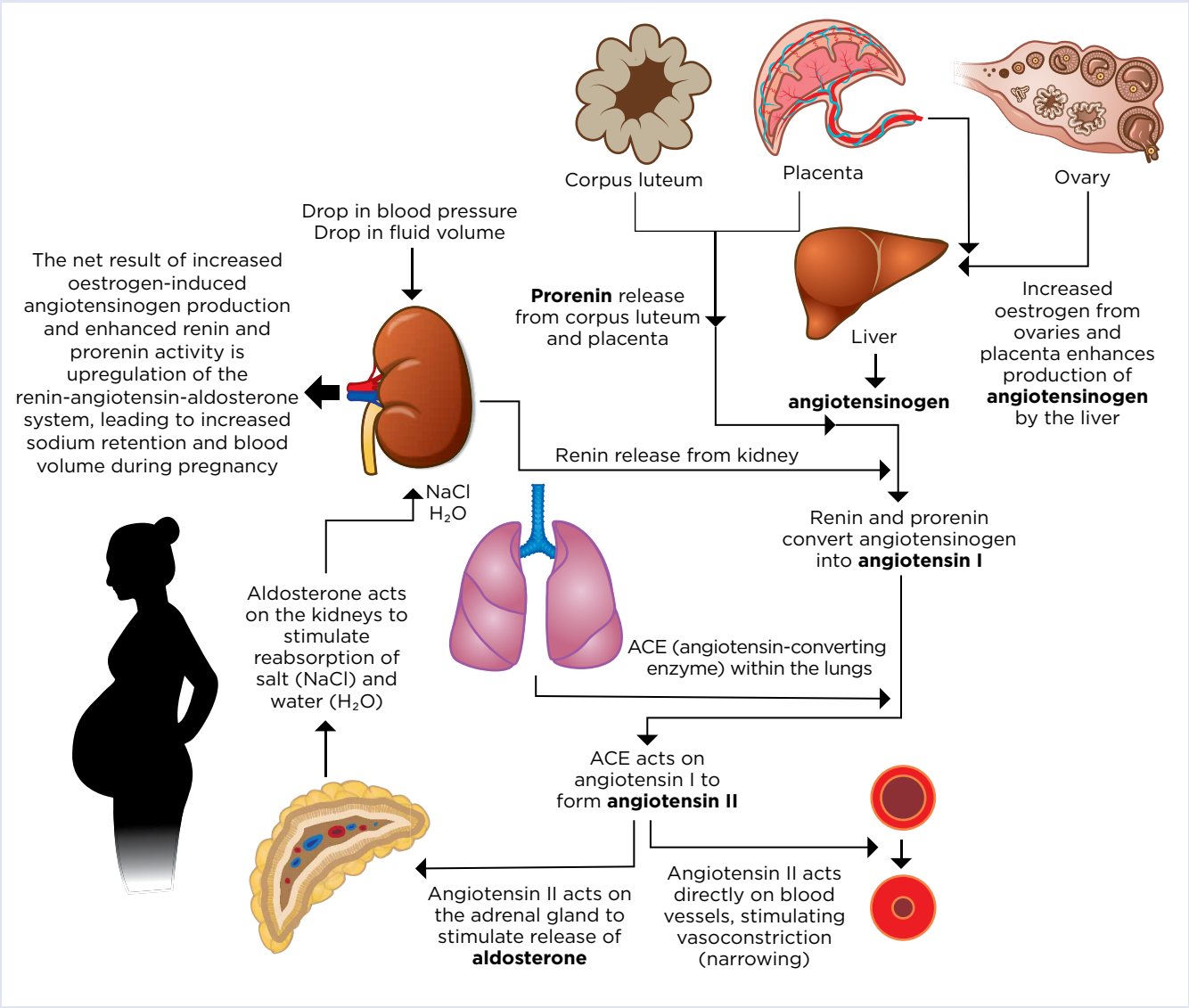
Haemodynamic changes

An increased blood volume is essential during pregnancy to supply extra blood to the foetoplacental unit and expanding maternal organs, such as the breasts, uterus, skin, and kidneys. The average adult female has around 4.3L of blood and this typically increases by around 40-50% during a uniparous (singleton) pregnancy. A recent meta-analysis study examined blood volume changes in 347 women across the three trimesters of normal (uncomplicated) pregnancies and noted volume increases of 6% in the first trimester, rising to 26% in the second and peaking at 48% in the third trimester just prior to delivery (Aguree and Gernand, 2019)

Role of the renin-angiotensin-aldosterone system (RAAS) in increasing blood volume

The RAAS is one of the major physiological mechanisms for regulating blood volume and blood pressure. It is usually activated following a drop in blood pressure (Fig 1) and quickly acts to restore blood volume and pressure. The RAAS is centred around the plasma protein

Fig 1. **Changes in the renin-angiotensin-aldosterone system during pregnancy**



angiotensinogen, which is continuously synthesised and released by the liver. When the kidneys detect a drop in blood pressure, they produce the enzyme renin, which rapidly converts angiotensinogen into a biologically inactive protein called angiotensin I. This circulates in the plasma until it reaches the lungs; here the angiotensin-converting enzymes (ACEs) convert it into biologically active angiotensin II. This is a potent vasoconstrictor, which acts directly on the smooth muscle layer of arteries, inducing contraction and reducing vessel diameter, thereby helping to restore blood pressure. Angiotensin II also simultaneously stimulates the release of aldosterone from the adrenal cortex.

Aldosterone is a steroid hormone that promotes the reabsorption of sodium (Na^+) ions in the kidney, thereby increasing the plasma sodium concentration (Fig 1). This increases the osmotic potential of the blood, increasing the movement of water from the tissues into the blood vessels, increasing blood volume and blood pressure.

Oestrogen levels increase throughout pregnancy peaking in the third trimester (Morton and Teasdale, 2022). Increased oestrogen from the ovaries and placenta stimulates the release of additional angiotensinogen from the liver and enhances the release of renin from the kidney, which increases RAAS activity. Activation of the RAAS is further amplified by the release of prorenin – a precursor to renin which is produced by both the corpus luteum and placenta (Wiegel et al, 2021).

As can be seen in Fig 1, enhanced activity of the RAAS during pregnancy ultimately increases aldosterone secretion and sodium retention. It is primarily this increased plasma sodium that attracts additional water into the blood vessels by osmosis and leads to the greater blood volumes observed during pregnancy. Increases in blood volume are even greater in multiparous (multiple) pregnancies, with a twin pregnancy seeing around a further 10-20% extra blood volume compared to singleton pregnancies. Blood volumes in twin pregnancies typically peak around 67% higher than those prior to pregnancy (di Marco et al, 2023). Increased blood volume undoubtedly places an increased burden on the cardiovascular system and contributes to the extra 10kg-12.5kg (22lb-28lb) of weight carried by expectant mothers during a typical pregnancy (NHS, 2023).

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"During pregnancy having hypercoagulable blood is inevitable as it is the normal physiological state"

Haemodilution of the blood and physiological anaemia of pregnancy

As plasma volume increases, it has the effect of gradually diluting the blood. This phenomenon is referred to as 'haemodilution of pregnancy' and peaks at around 32 weeks, with plasma levels quickly returning to normal six days post-delivery (Yanamandra and Chandraharan, 2012).

Haemodilution results in a progressive reduction in the packed red blood cell volume (haematocrit) throughout pregnancy (Fig 2). Before pregnancy, normal haematocrit scores range from 35-44%; scores fall to 31-41% in the first trimester, 30-39% in the second trimester and 28-40% in the final trimester (Morton, 2021).

This relative reduction in the volume of circulating erythrocytes (red blood cells) per unit of blood reduces the oxygen-carrying capacity of the blood and is often referred to as 'physiological anaemia of pregnancy'. These effects contribute to the increased fatigue and shortness of breath on exertion that are experienced by many pregnant women (Sanghavi and Rutherford, 2014).

Pathological anaemias

Pathological anaemias, which are also often referred to as true anaemias, occur when there are insufficient circulating erythrocytes to allow the efficient transport of oxygen and carbon dioxide. This may be due to reduced production of erythrocytes due to dietary insufficiency, destruction of erythrocytes, or erythrocyte loss through haemorrhage.

Anaemia is the most common haematological pathology experienced during pregnancy and, in developed countries, is seen in 10-20% of pregnant women. It has detrimental effects on both mother and foetus, and is responsible for up to 20% of maternal deaths in poorer developing countries (Chowdhury et al, 2014). According to the National Institute for Health and Care Excellence (NICE) (2023a), pregnant women should be offered screening for anaemia, with haemoglobin (Hb) levels of <110g/L throughout pregnancy being diagnosed as anaemia. Levels below this threshold should be investigated further and, where necessary, appropriate dietary supplementation should be prescribed.

The most common causes of anaemia are a lack of iron, cobalamin (vitamin B12) or folate (vitamin B9) in the diet or reduced efficiency of nutrient absorption in the gut during pregnancy (see part four of this series for further details).

Iron requirements increase by around two to three times the amount during pregnancy to:

- Allow for increased erythropoiesis (red blood cell production) in the mother;
- Supply the iron essential for the developing embryo, whose liver will be beginning the process of producing its own erythrocytes.

Additionally, maternal requirements for vitamin B12 increase by around two times the amount and vitamin B9 (folate) requirements increase by 10 to 20 times the amount (Soma-Pillay et al, 2016). Both these vitamins are essential for erythropoiesis in the mother and foetus, and dietary deficiency can lead to either cobalamin or folate deficiency anaemias in the mother and cause serious health and developmental problems in the developing foetus. Some women may also have undiagnosed pernicious anaemia, an autoimmune disease, which affects the gastrointestinal tract and leads to poor absorption of cobalamin (B12), leading to reduced B12 levels even when the vitamin is plentiful in the diet (Htut et al, 2021).

Maternal signs and symptoms of physiological anaemia in pregnancy and pathological anaemias are often very similar; they include (Turner et al, 2022):

- Increased heart rate (occasionally tachycardia – a resting heart rate above 100 beats per minute (bpm));
- Lethargy and generally feeling 'washed out';
- Shortness of breath, increased breathing rate (tachypnoea);
- Pale skin and mucous membranes;
- Skin lesions.

Although nothing can be done to alleviate the haemodilution responsible for the physiological anaemia of pregnancy, true anaemias should always be addressed. Pregnant women should be encouraged to increase their intake of iron, vitamin B12 and folate-rich foods and, where necessary, be prescribed dietary supplements.

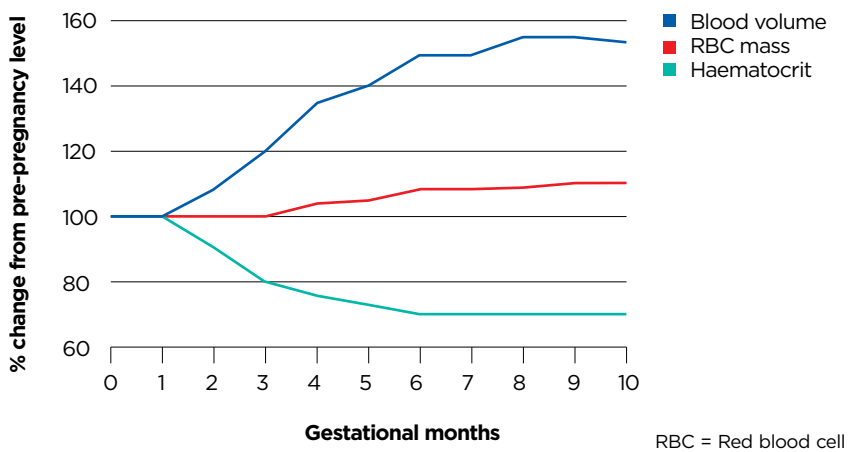
The use of supplements is often continued following delivery, particularly in mothers who are breastfeeding (National Academies of Sciences, Engineering, and Medicine Health and Medicine Division; Food and Nutrition Board, 2020). Supplementing the diet of pregnant women with iron tablets can be problematic in some women as it can contribute to the increased risk of constipation that comes with pregnancy (Astuti et al, 2023).

Cardiovascular changes

Changes to cardiac output

To circulate an increased volume of diluted blood the heart must work harder, so cardiac output (the amount of blood pumped per minute) increases throughout pregnancy. A detailed meta-analysis study by Meah et al (2016) revealed that cardiac output reaches its peak of 1.5L of blood per minute in the early third trimester; this is around 31% greater than that which is found in women who are not pregnant. This increase ensures adequate profusion of the placenta and the expanding uterus, and contributes to the enlargement and engorgement of organs, such as the breasts and kidneys, during pregnancy.

Fig 2. **Haematologic changes during pregnancy**



RBC = Red blood cell

Changes to heart size and position

To maintain increased cardiac output the muscular layer of the heart (the myocardium) has to work harder and enlarges. This is the normal physiological response of muscle to increased load, and the pumping chambers of the heart (ventricles) show marked hypertrophy (thickening) and heart rate increases typically by 10-20bpm (Soma-Pillay et al, 2016). This hypertrophy is readily observable when pregnant women undergo routine echocardiography and is particularly prominent in the left ventricle, which pumps blood through the systemic circulation (Afari et al, 2021).

As the uterus expands, the abdominal organs are pushed upwards (Fig 3), which displaces the diaphragm, shifting the heart so that it occupies a slightly higher position within the thorax (Bhatia and Chhabra, 2018; Yanamandra and Chandraharan, 2012). Following delivery of the baby, as blood volume and cardiac output return to their pre-pregnancy norms and the uterus gradually shrinks back to its original size, the myocardium will thin and the heart return to its original size and position within the thorax.

Changes to blood pressure

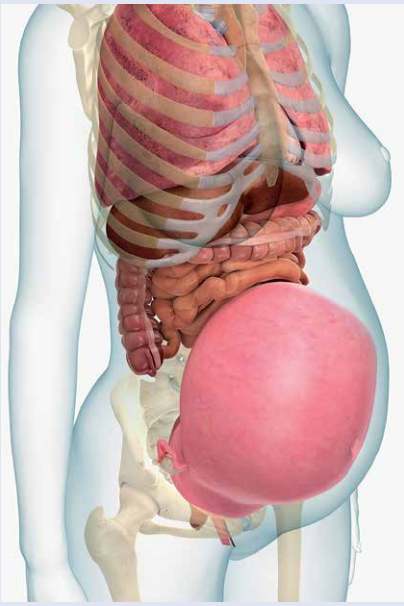
To accommodate the increase in blood volume during pregnancy, dilation of blood vessels is essential. One of the key functions of progesterone – and, to a lesser extent, oestrogen – is to promote the relaxation of the tunica media (smooth muscle layer) of blood vessels, resulting in general vasodilation. This leads to a drop in systolic, diastolic and mean arterial blood pressure.

Blood pressure falls fastest in the first trimester and typically reaches its lowest point in the second trimester, with drops of between 5mmHg and 10mmHg below pre-pregnancy levels being regarded as normal (Taranikanti, 2018). In most women, blood pressure then begins to increase in the final trimester and is back to normal pre-pregnancy values a couple of weeks after delivery (Mahendru et al, 2014). Being overweight when pregnant is associated with higher blood pressure, with women with a high body mass index (BMI) typically displaying both higher systolic and diastolic blood pressure throughout pregnancy (Rebelo et al, 2015).

Risk of preeclampsia

These normal changes to blood pressure are not experienced in all pregnant women, with around 3-5% experiencing

Fig 3. **Uterus expansion during pregnancy**



increases in blood pressure, which are indicative of preeclampsia (Fox et al, 2019). The diagnostic criterion for preeclampsia varies in developed countries with NICE currently defining the condition as a new-onset hypertension blood pressure ≥140mmHg systolic and/or ≥90mmHg diastolic, occurring in a pregnant woman after 20 weeks' gestation, usually with new onset proteinuria (presence of protein in the urine) (Walker and Morley, 2023). Not all women with preeclampsia will show symptoms, highlighting the importance of effective screening by health professionals. Where symptoms are present, they commonly include:

- Headache;
- Nausea;
- Visual disturbances;
- Pain below the ribs;
- Swelling of the hands, face, and feet. (NHS, 2021a).

Hypertension associated with preeclampsia is potentially physically damaging to both the mother and foetus, increasing the risk of haemorrhagic stroke, seizures, and kidney damage in the mother as well as increasing the risk of low birth weight babies, miscarriage and stillbirth. It is also recognised as being responsible for 20-30% of all preterm births (Fox et al, 2019). Yearly it is estimated that around 500,000 foetal deaths and 70,000 maternal deaths occur worldwide as a result of preeclampsia (Rana et al, 2019).

Preeclampsia and other hypertensive states associated with pregnancy require careful management as some of the mainstay antihypertensive medications used to lower blood pressure, such as many angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, are potentially teratogenic (can cause birth defects). In the UK the beta blocker labetalol is commonly used to reduce blood pressure in preeclampsia. Unlike most beta blockers, it has a minimal effect in slowing the heart rate and exerts most of its antihypertensive effects by dilating blood vessels and lowering peripheral resistance (Miller et al, 2022). Currently, labetalol is the only medication specifically licensed in the UK to treat hypertension in pregnant women (NICE, 2023b).

Despite decades of research the exact causes of preeclampsia remain uncertain, but it appears to be linked to problems associated with placental blood supply and development (NHS, 2021b). It is often quoted that the only cure for preeclampsia is birth, and this frequently means that babies will be delivered early at around 37 to 38 weeks, usually by an induced labour or Caesarean section. If the mother or baby is in danger it may be necessary to deliver before week 37. These premature births are more risky and, following delivery, the baby may need to spend time in a neonatal intensive care unit (NHS, 2021b).

Women planning on becoming pregnant should be encouraged to maintain their body weight within their normal recommended healthy range since a high BMI not only increases the risk of high blood pressure during pregnancy, but obesity is now recognised as being a major modifiable risk factor for developing preeclampsia and other maternal hypertensive states (Wang and Yang, 2021).

Potential for underlying heart disease to be revealed during pregnancy

The increases in blood volume and cardiac output seen in a normal pregnancy put additional strain on the heart and, for the first time, women may experience signs and symptoms of underlying heart disease. Recent figures suggest that up to 4% of pregnant women are affected by complications associated with cardiac disease during pregnancy (Mohamad, 2022). Indeed, in the US, cardiovascular disease is reported to be the leading cause of death during pregnancy and in the postpartum period, with women of colour and from lower-income households most at risk (Mohamad, 2022).

The most common cardiac conditions seen among pregnant women worldwide

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include cardiomyopathies, valve disease, coronary artery disease and pregnancy-associated myocardial infarction. Many of these may be associated with prior history of hypertension, poorly managed diabetes, alcohol abuse, smoking, and obesity (Iftikhar and Biswas, 2022).

Increased risk of thrombosis and emboli

It has long been known that pregnancy is associated with an increased risk of thrombosis (clot formation). The major reason for this is that the production of fibrinogen and other clotting factors increases throughout pregnancy (Tlamcani et al, 2018). Having hypercoagulable blood during pregnancy is advantageous since it prepares the mother's body for labour, allowing rapid coagulation of blood and the formation of fibrin clots which help seal off broken blood vessels and minimise the chance of major haemorrhaging at the time of delivery.

Virchow's triad

Virchow's triad (Fig 4) is a combination of three factors which, when present together, increase the risk of thrombosis (Kushner et al, 2022). These are:

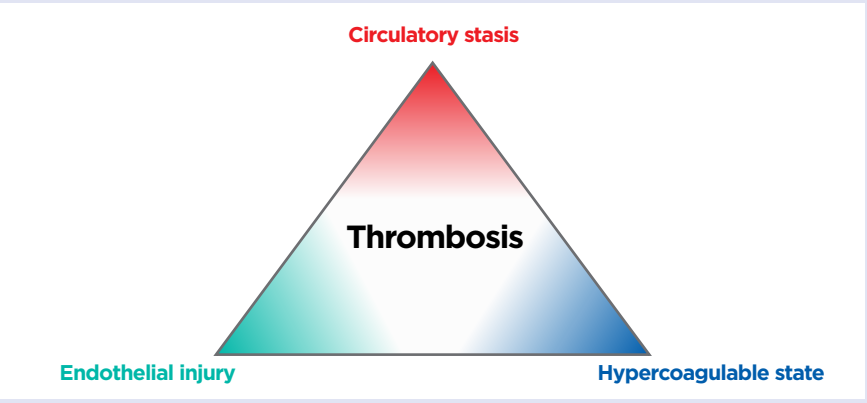
- Hypercoagulable blood;
- Blood vessel (endothelial) damage;
- Static blood (altered blood flow).

During pregnancy having hypercoagulable blood is inevitable as it is the normal physiological state. However, good advice from health professionals can reduce the chances of activating the other two points of Virchow's triad and, thereby, decrease the risk of potentially fatal thromboembolic events.

Lower limb oedema, venous insufficiency and venous stasis

A common feature of pregnancy is swelling of the legs, particularly around the ankles, with up to 80% of pregnant women displaying this so-called physiologic gestational oedema to varying degrees. This occurs for many reasons including increased blood volume and elevation of pregnancy hormones, which encourage water retention and enhance vascular permeability. Simultaneously there is compression of pelvic veins and the inferior vena cava (the major vein in the lower body) by the uterus as it expands (Dalio et al, 2022). These changes lead to venous insufficiency where blood does not flow adequately away from the legs. Progressively, circulation through the veins of the leg can become sluggish and eventually stop, resulting in venous stasis (Kearsley and Stocks, 2021); this activates a second point on Virchow's triad (Fig 4).

Fig 4. **Virchow's triad**



Women should be encouraged to keep active during their pregnancy since contraction of leg muscles will compress veins and, in this way, the skeletal muscle pump can help keep blood flowing and reduce the risk of static blood (venous stasis). Other methods to help with venous insufficiency and reduce the risk of venous stasis include leg elevation to use gravity's effects to encourage blood flow away from the legs, compression stockings, and foot massage.

Endothelial damage

Multiple toxins found in cigarette smoke are known to damage the lining (endothelium) of blood vessels, potentially activating the third point of Virchow's triad (Hahad et al, 2023). Therefore, pregnant women should be encouraged to quit smoking during their pregnancy, not just for the health of their unborn babies but also to significantly reduce their risk of thrombosis.

Other causes of endothelial damage include hypertension and physical damage to blood vessels caused by surgery. During labour blood vessels are invariably damaged and since surgical procedures are often required during delivery (Caesarean section/episiotomy) this third point of Virchow's triad (endothelial damage) is commonly activated, increasing the risk of thrombosis post-delivery.

Venous insufficiency (see section above) increases the risk of developing varicose veins since blood can accumulate in the veins of the legs, particularly the saphenous veins, which then expand and dilate and become progressively more visible as they fill with dark deoxygenated blood (Cohain, 2018). The reported prevalence of varicose veins in pregnant women varies widely between 20% and 60%, with pregnancy recognised as a major risk factor in their development (DeCarlo et al, 2022). The stretching of a varicose vein can physically damage the endothelial lining and the semi-lunar valves within the vessel. Endothelial damage inflicted by toxins in cigarette smoke or via surgical interventions or the formation of varicose veins all have the potential of activating the third point of Virchow's triad.

Potential for stroke, DVT and embolism

The enhanced coagulability of the blood means that pregnancy is associated with an increased risk of clot formation in both the cerebral circulation (cerebral thrombosis), leading to ischaemic stroke, and in the veins of the legs, leading to deep vein thrombosis (DVT), which has an associated risk of subsequent embolism formation. It has been estimated that strokes occur in around 30 out of every 100,000 pregnancies (Miller and Leffert, 2020).

Miller et al's (2016) research indicated that although older pregnant women experience more strokes than younger pregnant women, this appears to be an age-related effect rather than being related to pregnancy. However, in younger women, pregnancy itself appears to be a major risk factor for stroke. The authors of this study found around 18% of all strokes that occurred in women aged <35 years were associated with pregnancy; in contrast only around 1.4% of strokes in older women of childbearing age were associated with pregnancy (Miller et al, 2016).

The risk of venous thromboembolism (VTE) is increased by up to six times in pregnant women, with an incidence of around 12.2 per 10,000 compared with 2 per 10,000 in non-pregnant women (Nichols et al, 2020). Around 75-80% of VTE events take the form of deep vein thromboses (the

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majority being in the left leg), with the remaining 20-25% potentially deadly pulmonary emboli (James, 2009).

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is a rare but serious condition, which involves general activation of the blood clotting cascade and the formation of thrombi (clots) throughout the body. DIC is reported to occur in between 0.03% and 0.35% of pregnancies and usually occurs as a complication of other maternal pathologies, such as preeclampsia, haemolysis, elevated liver enzymes and low platelets syndrome (see part four of this series); retained stillbirth; sepsis; and postpartum haemorrhage. All of these can activate the clotting cascade.

DIC can lead to multiple organ failure and tissue necrosis as small blood vessels become blocked, depriving tissues of oxygen and nutrients. Paradoxically the formation of multiple thrombi throughout the body can exhaust the plasma clotting factors, also increasing the risk of haemorrhages. Management of DIC is multifaceted and involves careful monitoring of blood parameters, transfusions, organ support and surgery (Erez et al, 2022).

"Many countries have recommended anticoagulation therapy in pregnant women with confirmed Covid-19 infection"

Recently, with the advent of the Covid-19 pandemic, many pregnant women have become infected. Since Covid-19 is known to increase the risk of thromboembolic events and pregnancy is associated with a hypercoagulable state, many countries have recommended anticoagulation therapy in pregnant women with confirmed Covid-19 infection (Varlas et al, 2023). In the UK, the current advice from the Royal College of Obstetricians and Gynaecologists (RCOG) – namely, RCOG (2022) – is that pregnant women admitted with confirmed or suspected Covid-19 on low-flow oxygen and at low risk of bleeding should be offered a therapeutic dose of low molecular weight heparin for thromboprophylaxis, unless birth is expected within 24 hours.

Conclusion

In this first article in the series, we have explored some of the key changes to the blood and cardiovascular system that take place during pregnancy and highlighted some of the common problems and pathophysiologies that are associated with these changes. **NT**

- The second article in this series will explore changes to the respiratory and urinary systems during pregnancy.

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