Section 1 Physiological Changes in Pregnancy

Chapter 1

Normal Cellular Changes during Pregnancy and the Puerperium

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Introduction

There are both subtle and substantial changes in hematological parameters during pregnancy and the puerperium, orchestrated by changes in the hormonal milieu. A thorough understanding of these is important to avoid both over- and under-diagnosing abnormalities. Some of the quoted reference ranges may differ among centers, depending on laboratory techniques. However, the principles of recognizing physiological changes can still be applied.

Red Cells

During pregnancy, the total blood volume increases by 1.5 L, mainly to supply the needs of the new vascular bed. Almost 1 L of blood is contained within the uterus and maternal blood spaces of the placenta. Expansion of plasma volume by 25–80% is one of the most marked changes, reaching its maximum by mid-pregnancy. Red cell mass also increases by 10–20%, but the net result is that hemoglobin (Hb) concentration falls[1]. Typically, this is by 10–20 g/L by the late second trimester and stabilizes thereafter. Women who take iron supplements have less pronounced Hb changes, as they increase their red cell mass proportionately more than those without dietary supplements; typically, the increase is 30% over pre-pregnancy values[1].

It is hard to define a normal reference range for Hb during pregnancy and the limit for diagnosing anemia. The World Health Organization has suggested that anemia is present in pregnancy when Hb concentration is <110 g/L. However, large studies in healthy Caucasian women taking iron supplements from mid-pregnancy found Hb values in the early third trimester to be 104–135 g/L (2.5th–97.5th centiles)[2]. A randomized, placebo-controlled trial of iron supplementation in pregnancy found that Hb levels in those who had received 66 mg ferrous iron per day from 9 to 18 weeks' gestation were significantly higher from the beginning of the second trimester to 8 weeks postpartum[3].

Studies from other ethnic populations have documented lower third trimester Hb concentrations, which may be attributable to the women entering pregnancy with poor iron stores or with dietary deficiencies of iron and folic acid. However, a study of healthy women in China who were all given iron, folate, and vitamin B_{12} supplements during pregnancy found Hb levels of 95–130 g/L in the second trimester and 96–135 g/L in the third trimester (5th–95th centiles), so there may be genuine racial differences[4].

Women living at an altitude of 2240 m above sea level in Mexico City were found to have a progressive drop in Hb levels during pregnancy, from 122 to 152 g/L in the first trimester to 111–138 g/L in the early third trimester and 108–142 g/L by term (5th–95th centiles)[5]. All these women took iron, folate, and vitamin B_{12} supplements. The progressive drop in Hb was similar to what has been observed in other studies on women not given iron supplements during pregnancy[3]. Although altitude hypoxia stimulates erythropoiesis, it is not known what effect altitude has on plasma volume expansion in pregnancy. Other studies from even higher altitudes, up to 4340 m above sea level, have confirmed that Hb levels progressively drop as gestation advances, rather than stabilizing after the second trimester[5].

Red cell count and hematocrit (Hct) values are likewise lower in pregnancy, but the other red cell indices change little (Table 1.1), although red cells show more variation in size and shape than in the non-pregnant state. There is a small increase in mean cell volume (MCV), on average 4 fL for iron-replete women, which reaches a maximum at 30–35 weeks' gestation and occurs independently of any deficiency of B_{12} and folate[2]. Hemoglobin and hematocrit increase after delivery. Significant increases have been documented between measurements taken at 6–8 weeks postpartum and those at 4–6 months postpartum, demonstrating that this length of time is needed to restore them to non-pregnant values[1].

Table 1.1 Red cell indices during pregnancy and the puerperium

Red cell indices	Gestation			
	18 weeks	32 weeks	39 weeks	8 weeks postpartum
Hemoglobin (Hb) g/L	119 (106–133)	119 (104–135)	125 (109–142)	133 (119–148)
Red cell count × 10^{12}/L	3.93 (3.43–4.49)	3.86 (3.38–4.43)	4.05 (3.54–4.64)	4.44 (3.93–5.00)
Mean cell volume (MCV) fL	89 (83–96)	91 (85–97)	91 (84–98)	88 (82–94)
Mean cell hemoglobin (MCH) pg	30 (27–33)	30 (28–33)	30 (28–33)	30 (27–32)
Mean cell hemoglobin concentration (MCHC) g/dL	34 (33–36)	34 (33–36)	34 (33–36)	34 (33–36)
Hematocrit	0.35 (0.31–0.39)	0.35 (0.31–0.40)	0.37 (0.32–0.42)	0.39 (0.35–0.44)

Mean and reference ranges (2.5th–97.5th centiles). Samples were collected longitudinally from 434 women. Adapted from Ref. [2].

Table 1.2 Hematinic factors during pregnancy and the puerperium

Hematinic factors	Gestation			
	18 weeks	32 weeks	39 weeks	8 weeks postpartum
Serum ferritin (μg/L)	32 (8–123)	18 (6–48)	21 (7–64)	46 (15–144)
Plasma folate (nmol/L)	15 (6–34)	10 (5–22)	10 (4–22)	9 (4–22)
Erythrocyte folate (μmol/L)	0.85 (0.46–1.59)	0.76 (0.41–1.40)	0.66 (0.33–1.33)	0.55 (0.29–1.01)
Plasma B_{12} (pmol/L)	216 (96–484)	169 (73–388)	154 (71–333)	315 (148–672)

Mean and reference ranges (2.5th–97.5th centiles). Samples were collected longitudinally from 434 women. Adapted from Ref. [2].

Changes in hematinic factors are shown in Table 1.2. Red cell folate levels have been shown in some studies to decrease during pregnancy, but in others to increase; plasma or serum folate levels always decrease during pregnancy[2,6]. These differences probably relate to dietary intake of folic acid or use of supplements. Folate levels may be low in the puerperium, especially in those who breast-feed. Vitamin B_{12} levels decrease during pregnancy, but recover by 6–8 weeks postpartum[2,6]. Iron stores, as judged by serum ferritin levels, become depleted in pregnancy, even when iron supplements are given, but are restored to early pregnancy levels by 5–8 weeks after delivery[2,7].

Summary Points

- Hb concentrations decrease in pregnancy.
- Hb <104 g/L suggests anemia.
- Hb >135–g/L is unusual and suggests inadequate plasma volume expansion (which can be associated with pregnancy problems including pre-eclampsia and poor fetal growth) or rarely a myeloproliferative disorder.
- MCV is normally slightly increased.
- MCH and MCHC are normally unchanged in pregnancy and do not change with gestation.
- Iron stores become depleted during pregnancy.
- B_{12} levels may be very low during pregnancy.
- Folate levels may decrease during pregnancy, depending on dietary intake.

White Cells

The white cell count (WBC) is increased in pregnancy [2], with a typical reference range of 6–16 × 10^9/L (Figure 1.1). Supplementation with iron and folate does not affect the total white cell count during or after pregnancy. In the hours after delivery[8], healthy women have been documented as having a WBC of 9–25 × 10^9/L. These naturally high WBCs have implications for the diagnosis of sepsis, especially during labor or soon after delivery[9]. White cell counts may also be transiently elevated after administration of corticosteroids in pregnancy, such as those given to promote fetal lung maturity when premature delivery is anticipated. By 4–8 weeks post-delivery, typical WBC ranges are similar to those in healthy non-pregnant women (4–10 × 10^9/L).

There has been much discussion about the normal ranges for the different types of white cells (Table 1.3) [8,10,11]. Neutrophils contribute most to the overall higher WBC. There is an increase in immature forms

Table 1.3 Total and differential white cell count in late pregnancy and the early puerperium

	Total and differential white cell count			
	Week 33 (n=151)	**Week 36 (n=146)**	**Week 39 (n=130)**	**1–3 hours post-delivery (n=91)**
Total white cell count × 10^9/L	9.1 (5.7–14)	8.9 (6.1–15)	9.0 (6.0–16)	16 (9.4–25)
Neutrophils × 10^9/L	6.5 (3.5–11)	6.4 (4.1–11)	6.5 (3.7–13)	14 (6.6–23)
Lymphocytes × 10^9/L	1.7 (0.9–2.8)	1.8 (1.1–2.8)	1.8 (1.1–2.9)	1.1 (0.5–2.4)
Monocytes × 10^9/L	0.50 (0.2–1.0)	0.50 (0.3–1.0)	0.50 (0.28–0.90)	0.53 (0.3–1.2)
Eosinophils × 10^9/L	0.10 (0.0–0.40)	0.10 (0.0–0.30)	0.10 (0.0–0.40)	0.0 (0.0–0.50)
Basophils × 10^9/L	0.0 (0.0–0.10)	0.03 (0.0–0.10)	0.04 (0.0–0.10)	0.08 (0.0–0.20)

Median and reference ranges (2.5th–97.5th centiles). From a longitudinal study of 154 women who were taking iron supplements during pregnancy and had undergone at least one previous normal pregnancy. Post-delivery samples were excluded for cases delivered by cesarean section. Adapted from Ref. [8].

	18 weeks (n=422)	32 weeks (n=297)	39 weeks (n=264)	8 weeks postpartum (n=166)
2.5th centile	5.6	6	5.8	3.9
Mean	8.8	9.7	9.3	6.1
97.5th centile	13.8	15.7	15.1	9.7

Figure 1.1 Normal values for white cell counts during pregnancy. Mean and reference ranges (2.5th –97.5th centiles). Samples were collected longitudinally from 434 women. Adapted from ref [2].

and the cytoplasm shows toxic granulation. The count is relatively constant throughout gestation (3– 10 × 10^9/ L), markedly elevated in the hours after delivery (up to 23 × 10^9/L) and back to non-pregnant values by 4–8 weeks postpartum (1.5–6 × 10^9/L). Neutrophil chemotaxis and phagocytic activity are depressed, the latter being inhibited by factors present in pregnancy serum. There is also evidence of increased oxidative metabolism in neutrophils during pregnancy.

The lymphocyte count decreases during pregnancy through the first and second trimesters, increases during the third trimester, but remains low in the early puerperium as compared to normal non-pregnant values[8,10,11]. The typical pregnancy range for lymphocyte count is from 1.1 × 10^9/L to 2.8 × 10^9/L, compared with the non-pregnant reference range of from 0.8 × 10^9/L to 4.0 × 10^9/L. The lymphocyte count is restored to normal range by 4–8 weeks after delivery.

Detailed studies of T- and B-lymphocyte subsets in peripheral blood and the proliferative responses of these cells to mitogens found more helper and suppressor cells and less killer cells during pregnancy. Lymphocyte proliferation in response to a variety of agents was found to be impaired in pregnancy, suggesting that there is an immunosuppressant factor present.

The monocyte count is higher in pregnancy, especially in the first trimester[8,10,11]. Typical values in the third trimester are 0.2–1.0 × 10^9/L, as compared to non-pregnant values of 0.1–0.9 × 10^9/L. The monocyte to lymphocyte ratio is markedly increased in pregnancy. The eosinophil count does not change significantly during pregnancy (0.03–0.5 × 10^9/L) [8,11]. The basophil count has been found in one study to be low in the second trimester[11], but in a detailed study during the third trimester and early puerperium[8], levels were similar to those found in non-pregnant subjects (up to 0.1 × 10^9/L). Myelocytes and metamyelocytes may be found in the peripheral blood film of healthy women during pregnancy and do not have pathological significance.

Summary Points

- WBC is elevated in pregnancy, mostly due to neutrophilia.
- Lymphocyte count is lower and monocyte count higher.
- During pregnancy, only WBC >16 × 10^9/L is considered abnormal.
- Soon after delivery, only WBC >25 × 10^9/L is considered abnormal.
- Eosinophil and basophil counts do not change significantly in pregnancy.

Platelets

Like the red cell mass, the platelet mass increases in pregnancy but not to the same extent as the plasma volume, so that the platelet count appears to fall in a full blood count. Large cross-sectional studies in pregnancy of healthy women (specifically excluding any with hypertension) have shown that there is also a left-shift of the platelet count distribution histogram. Thus, platelet counts are lower during pregnancy (Table 1.4), particularly in the third trimester[12,13]. This is termed "gestational thrombocytopenia." Almost 12% of women in one study[13] were found to have a platelet count of <150 × 10^9/L late in pregnancy. Of these women, 79% had platelet counts of 116–149 × 10^9/L; none had complications related to thrombocytopenia and none of their babies had severe thrombocytopenia (platelet count <20 × 10^9/L). Thus, it has been recommended that the lower limit of platelet count in late pregnancy should be considered as 115 × 10^9/L. Less than 1% of healthy women in pregnancy have platelet counts of <100 × 10^9/L [12,13]. Platelet counts increase within 2–3 days of delivery in women with gestational thrombocytopenia[12].

Table 1.4 Platelet count in pregnant and non-pregnant women

Platelet count ×10^9/L	Pregnant women (n=6770)	Non-pregnant women (n=287)
Mean	213	248
Median	206	242
2.5th centile	116	164
97.5th centile	346	362
Count <150 × 10^9/L	11.6%	1.0%

Cross-sectional study of women in pregnancy, all 36 or more weeks' gestation; compared to healthy women of similar age. Adapted from Ref. [13].

Platelet size is an indicator of the age of the platelets; young ones are large and they become progressively smaller with age. Platelet volume has a skewed distribution, tailing off at larger volumes. The platelet volume distribution width increases significantly and continuously as gestation advances and the mean platelet volume becomes an insensitive measure of platelet size. Studies suggest that platelet lifespan is shorter in pregnancy. The decrease in platelet count and increase in platelet size in pregnancy suggests that there is hyper-destruction of platelets[14].

Platelet function, as assessed by the time required for whole blood to occlude a membrane impregnated with either epinephrine or adenosine 5′ diphosphate (ADP), has been studied in late pregnancy[15,16]. No correlation was found between platelet count and the "closure times" over a range of platelet counts of 44–471 × 10^9/L in healthy women[16]. Another study found that the closure times were increased in women with severe pre-eclampsia, although they did not correlate with clinical bleeding problems in these women [17]. In women with gestational thrombocytopenia,

platelet closure times are influenced by hemoglobin level, being prolonged when there is both thrombocytopenia and anemia[15]. This is perhaps not surprising, given the contribution of red cells to the hemostatic process, in part due to ADP donation. The increase in fibrinogen during pregnancy maintains platelet function, as fibrinogen is the ligand for platelet to platelet aggregation.

Summary Points

- Platelet count decreases during pregnancy in some patients.
- The lower limit of normal platelet count at term is 115×10^9/L.
- There is evidence of increased platelet destruction in pregnancy.
- Platelet closure times are not affected by absolute platelet count in healthy women during pregnancy.
- Platelet closure times are prolonged when there is anemia in addition to a low platelet count.
- The increase in fibrinogen during pregnancy more than compensates for the fall in platelet count.

Case Studies

Case Study 1
A woman was admitted for an elective cesarean section at 39 weeks. Her full blood count showed a platelet count of 90×10^9/L. She was not hypertensive, had no history of medical disorders and was not taking any medication other than pregnancy vitamin supplements. A repeat platelet count was requested (84×10^9/L) and a coagulation screen performed, which was normal. She had never been previously told that her platelet count was low and had never experienced unexplained bruising or significant bleeding complications, during childhood and early adulthood, nor at the time of her previous cesarean delivery, 3 years earlier. The laboratory records revealed a platelet count of 158×10^9/L in early pregnancy and 110×10^9/L at 28 weeks' gestation, but there were no records prior to confirmed pregnancy. Gestational thrombocytopenia with a low–normal platelet count at the start of pregnancy was diagnosed. The cesarean section went ahead under a spinal anesthetic. There were no anesthetic or surgical complications. After 48 hours, the platelet count was 110×10^9/L and 4 weeks later it was 194×10^9/L. This case illustrates how a falling platelet count during pregnancy became "noticed" because the absolute count was low enough to attract attention and surgical delivery was planned. The prompt rise in platelet count after delivery and subsequent normal-range value makes gestational thrombocytopenia the most likely diagnosis, rather than immune thrombocytopenia.

Case Study 2
A woman who had delivered with the assistance of obstetric forceps was reviewed on the postnatal ward the following morning. The midwife had taken a full blood count and was concerned about the results: hemoglobin 96 g/L, white cell count 22×10^9/L, platelet count 176×10^9/L. The bedside Modified Obstetric Early Warning Score chart was reviewed. In the 24 hours since delivery, temperature had been 36.9–37.4°C, pulse rate 80–95 beats per minute, respiratory rate 18–22 breaths per minute, blood pressure between 102/63 mmHg and 113/66 mmHg. Lochia were normal in amount and non-offensive. The uterus felt well contracted and was not tender. The woman complained of dysuria. A urine sample had shown 2+ blood, 1+ white cells, 1+ protein but was negative for nitrites and a sample had been sent to the laboratory for culture. The midwife questioned whether the high white cell count and complaints of dysuria indicated urinary tract infection, suggesting that antibiotics could be prescribed. However, none of the observations, bedside tests, or the full blood count were actually abnormal for a woman recently delivered and she seemed well. It was explained that the white cell count on its own did not indicate sepsis and a high white cell count was typical during labor and in the early puerperium. It was agreed that the result of the urinary culture would be awaited and that antibiotics would only be prescribed if this confirmed infection, or if continued observations of temperature, pulse, respiratory rate, or blood pressure became abnormal.

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Chapter 2

Normal Coagulation Changes during Pregnancy

Rachel Rayment

Introduction

During pregnancy, the hemostatic system alters in preparation for delivery of the fetus. In an uncomplicated vaginal delivery, bleeding is largely prevented by the mechanical events of uterine contraction and retraction of the interlacing myometrial fibers surrounding maternal spiral arteries of the placental bed. Myometrial contraction compresses the spiral arteries and veins, thereby obliterating their lumina[1]. As a result of myometrial contraction, the uterine walls are firmly opposed, providing further support for hemostasis. However, on occasion this process fails, e.g. uterine atony, placental abruption, placental retention, and bleeding occurs. The maternal blood supply to the placenta at term is 600–700 mL/min[2], and failure to occlude the blood supply at delivery results in catastrophic hemorrhage and consumption of coagulation factors. In preparation for this possibility, the normal balance of hemostasis alters, becoming prothrombotic and hypofibrinolytic. An unfortunate consequence of this is an increased incidence of venous thrombotic events during pregnancy and the puerperium. This chapter will discuss the changes in hemostasis seen during normal pregnancy, and the role of coagulation tests in its assessment.

Primary Hemostasis

Primary hemostasis is the initial response of the body to a breach in the integrity of the endothelium and is dependent on the interaction between von Willebrand factor and platelets. von Willebrand factor is anchored to the subendothelial matrix through collagen binding. It then binds circulating platelets which are recruited to the site of injury and ultimately form a temporary plug which both stops bleeding and serves to provide a phospholipid surface on which coagulation factors can function in order to form a more durable fibrin clot (Figure 2.1).

Defects in primary hemostasis result in a tendency toward mucocutaneous bleeding, in particular menorrhagia, and women with von Willebrand disease are at risk of postpartum hemorrhage. It is therefore perhaps unsurprising that von Willebrand factor rises during normal pregnancy. Estrogen directly stimulates endothelial cells to increase their rate of production of VWF[3], and this is thought to be the mechanism for the increase in pregnancy, where a doubling of levels may occur. Since von Willebrand factor is the carrier molecule for factor VIII, there is an equivalent increase in factor VIII levels by the third trimester of pregnancy. Levels of von Willebrand factor begin to fall around 3 days postpartum[4], returning to preconception levels in the subsequent 2–3 weeks. This may be associated with delayed postpartum hemorrhage in women with von Willebrand disease.

As discussed in Chapter 1, the platelet count is lower during pregnancy. In approximately 5% of pregnancies, the platelet concentration is reduced in the absence of any detectable pathology. This is thought to be due to consumption of platelets in the uteroplacental bed and is of no clinical consequence to either the mother or fetus. In this so-called gestational thrombocytopenia, the platelet count starts in general to fall in the second trimester and to plateau when the pregnancy reaches 36–37 weeks. The platelet count nadir is often above 100×10^9/L, but can be lower. In general, a platelet count below 80×10^9/L should be investigated for alternative causes, such as immune thrombocytopenia or a microangiopathic hemolysis. It is unlikely that a platelet count below 50×10^9/L is due to gestational thrombocytopenia alone[5]. Gestational thrombocytopenia does tend to recur with subsequent pregnancies and, where there has been some doubt about the etiology of the thrombocytopenia, this can be removed by simply checking the platelet count outside of pregnancy since complete recovery is

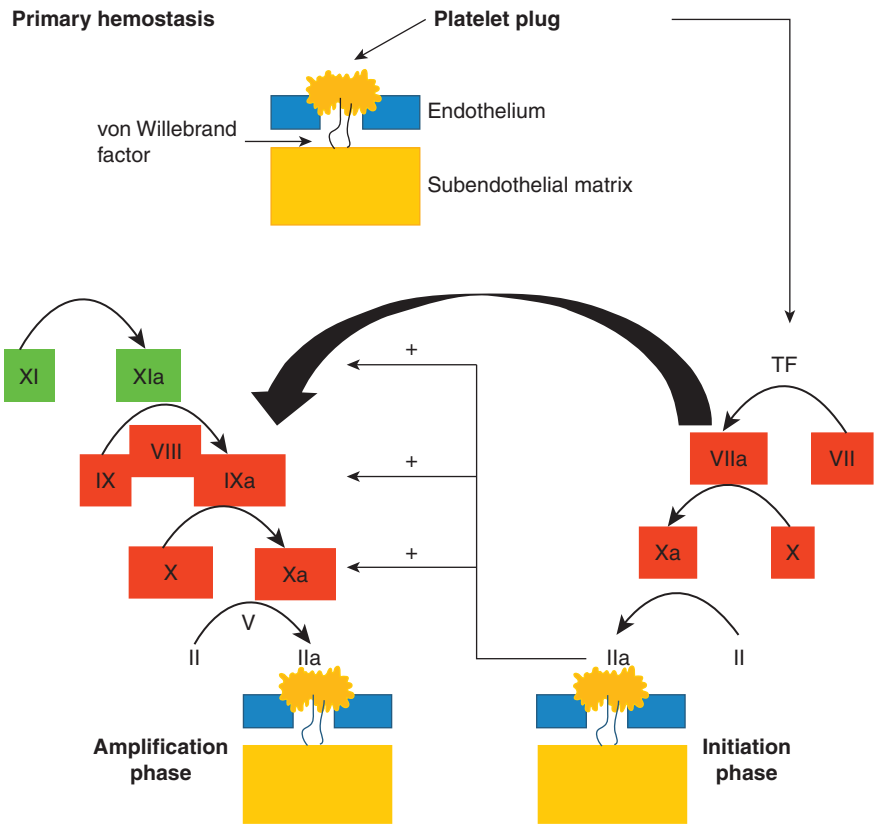

Figure 2.1 Thrombin generation and normal changes in coagulation in pregnancy. Following formation of a primary hemostatic plug tissue factor activates factor VII on the phospholipid surface created by activated platelets. Factor VII then activates factor X which cleaves prothrombin to thrombin. This sets off the amplification phase of coagulation, generating a "burst" of thrombin generation. Subsequent formation of fibrin glues the primary hemostatic plug through its interaction with platelets. Clotting factors which rise during pregnancy are highlighted in red, and those which may increase or decrease, in green.

to be expected, usually within days of delivery, but always within weeks.

Thrombin Generation

A primary platelet plug will disaggregate over time, since it is held together by non-covalent bonds. Tissue factor activates factors IX and X to enable production of thrombin and ultimately a fibrin clot at the site of a primary platelet plug. The process is largely controlled by thrombin, which not only cleaves fibrinogen to its fibrin monomer, but also activates coagulation factors, V, VIII, and XI, allowing the generation of a large "burst" of thrombin. Thrombin activity is limited to the site of need by the natural anticoagulants, protein C and antithrombin.

Thrombin generation is increased during pregnancy[6]. Many of the procoagulant factors increase during pregnancy, predominantly during the second trimester (Figure 2.1), although interestingly levels of prothrombin itself are unchanged during pregnancy [7]. This increased thrombin generation is evidenced by an increase in prothrombin fragments 1 and 2 (which result from the cleavage of prothrombin)[8] and thrombin–antithrombin complexes[9] (which are formed in the presence of free thrombin).

Coagulation factors have usually returned to pre-pregnancy levels by 4–6 weeks postpartum[10].

Fibrinogen

Fibrinogen is cleaved to fibrin monomer by thrombin. This "glue" binds the primary hemostatic plug, through its interactions with platelets. The fibrin clot is further stabilized through cross-linking by factor XIII. Fibrinogen concentration increases during pregnancy, the normal range rising from 2–4 g/L to 4–6 g/L. Fibrinogen is essential for hemostasis and in the event of bleeding is often the first coagulation factor to fall to critical levels[11]. At the time of delivery, the raised fibrinogen levels protect against bleeding, in an otherwise uncomplicated delivery. Fibrinogen levels have been shown to correlate with the likelihood of ongoing bleeding in the event of a postpartum hemorrhage[12] and a fibrinogen level >4 g/L is rarely associated with continued bleeding.

Factor XIII levels fall early in pregnancy, then gradually rise, such that levels are about 50% of baseline toward the end of pregnancy[13].

Fibrinolysis

Once fibrinogen has been cross-linked by factor XIII the clot is stable (allowing repair of the underlying endothelium) until it is broken down by an enzymatic process called fibrinolysis (Figure 2.2). In the presence of a fibrin clot, tissue plasminogen activator (tPA) cleaves plasminogen, generating plasmin, which in turn digests fibrin at exposed lysine residues, resulting in the formation of fibrin degradation products.

tPA is inhibited by plasminogen activator inhibitor (PAI). Outside of pregnancy the only detectable plasminogen inhibitor is PAI-1, which is produced by endothelial cells. However, during pregnancy the placenta produces PAI-2. Both PAI-1 and PAI-2 rise in pregnancy, thus creating a hypofibrinolytic state. Since PAI-2 is produced by the placental villous cells, placental and fetal wellbeing can affect levels of PAI-2 in pregnancy[14]. Levels fall following delivery and are back to pre-pregnancy levels by about 5 weeks postpartum[15,16]. Interestingly, although PAI is increased during pregnancy, one of the markers of fibrinolysis, the D-dimer, is often raised throughout pregnancy, reflecting the overall increase in fibrin production through pregnancy [7]. This causes difficulty in the clinical assessment of suspected venous thromboembolism, and there is currently an ongoing study ascertaining a normal range for D-dimers during pregnancy[17].

Fibrinolysis is also inhibited by thrombin-activatable inhibitor of fibrinolysis (TAFI). Plasmin binds to and digests fibrin on exposed lysine residues. TAFI removes the exposed binding sites, thus limiting the action of plasmin[18]. TAFI concentrations are unaffected by pregnancy[19]. Tranexamic acid is a lysine analog that binds to the lysine binding site on plasminogen and inhibits plasmin formation. It is used clinically to inhibit fibrinolysis and reduce bleeding.

Plasmin is also inhibited by the antifibrinolytics α2-antiplasmin and α2-macroglobulin. α2-antiplasmin levels are not affected in pregnancy in general, although they may sometimes increase[19]. A pregnancy-associated form of α2-macroglobulin has been reported, the levels of which rise significantly during the first trimester, persist throughout pregnancy, and fall 8 weeks postpartum[20].

Physiological Anticoagulants

The physiological anticoagulants include protein C, protein S, and antithrombin. These serine proteases serve to limit thrombin generation (Figure 2.3).

Thrombin generation is limited by the action of the natural anticoagulants, antithrombin, protein C, and its cofactor, protein S. Antithrombin binds free thrombin but also inactivates factors IXa, Xa, and XIa. Activated protein C inhibits factors Va and VIIIa.

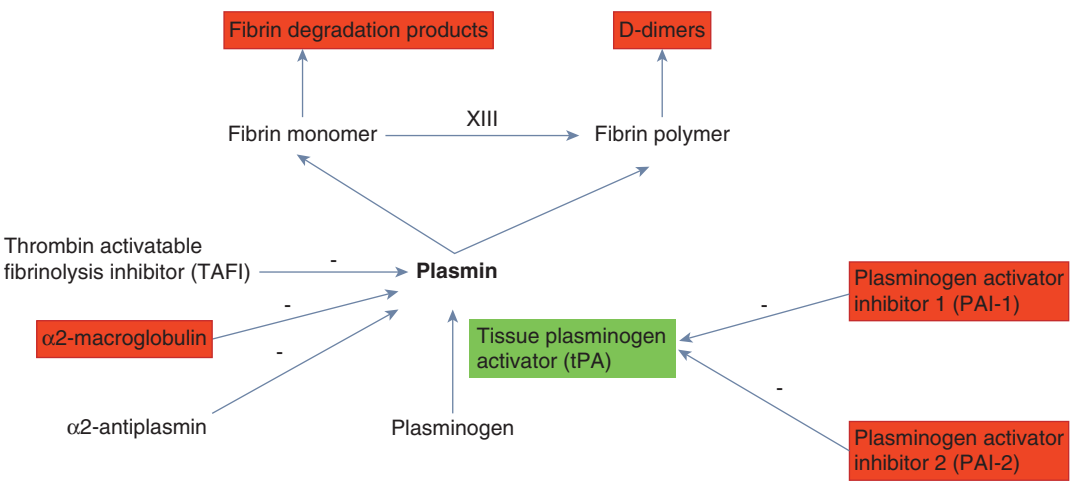

Figure 2.2 Fibrinolysis and the normal changes during pregnancy. Breakdown of fibrin is through the enzymatic action of plasmin and results in the formation of fibrin degradation products. Pregnancy is considered an altered fibrinolytic state, due to the increase in plasminogen activator inhibitors 1 and 2. Factors that rise during pregnancy are highlighted in red, and those that may decrease, in green.

Table 2.1 Changes in coagulation factors during pregnancy

		Comments
Factors that increase	VII	Levels have returned to pre-pregnancy levels by 4–6 weeks
	X	
	VIII	Factor VIII is carried by von Willebrand factor
	von Willebrand factor	Levels begin to fall 3 days following delivery, returning to baseline levels by 3 weeks
	Fibrinogen	Normal range in pregnancy increases to 4–6 g/L
	Plasminogen activator inhibitor (PAI) 1 and 2	PAI-2 is produced exclusively by the placenta Levels are reflective of placental function – are reduced in babies of low birth weight
	α2-macroglobulin	A pregnancy-associated form of α2-macroglobulin has been reported, the levels of which rise significantly during the first trimester, persist throughout pregnancy, and fall 8 weeks post-partum
Factors that do not change	V Thrombin (II) Protein C Antithrombin Tissue factor pathway inhibitor (TFPI) Thrombin activatable fibrinolysis inhibitor (TAFI)	
	α2-antiplasmin	May increase slightly
Factors that decrease	XI	May be unchanged or sometimes increase
	Protein S	Both free and bound protein S are reduced

While antithrombin and protein C are unchanged during pregnancy, protein S falls by up to 50% early in the second trimester, limiting the action of both activated protein C and tissue factor pathway inhibitor (TFPI) (Table 2.1).

Antithrombin by inhibiting thrombin, IXa, Xa, and XIa, serves to limit thrombin generation to the site of need. Antithrombin levels are unchanged during pregnancy[19].

Thrombin which is not clot-bound is also able to bind to thrombomodulin, which is expressed by the endothelium. This complex is then able to activate protein C which, in the presence of its cofactor protein S, inhibits both factor V and factor VIII. A proportion of protein S is bound to C4b-binding protein, and the activity of protein S is determined by the amount and activity of the free antigen. Protein C levels are unaffected by pregnancy but protein S levels fall early in the second trimester by as much as 50% due to altered binding to C4b-binding protein. Protein S levels remain low until delivery but return to baseline by 3 days following delivery[21]. Both free and bound protein S are reduced[22].

The activity of protein C can be measured in vitro by the activated protein C (APC) resistance

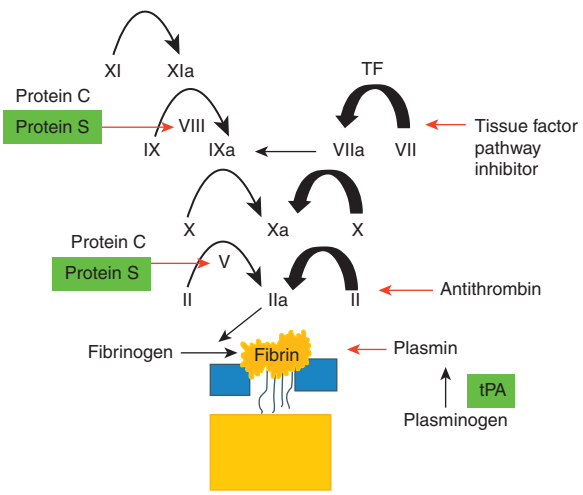

Figure 2.3 Natural anticoagulants and the normal changes during pregnancy. Thrombin generation is limited by the action of the natural anticoagulants, antithrombin, protein C, and its cofactor, protein S. Antithrombin binds free thrombin but also inactivates factors IX, X, and XI. Activated protein C inhibits factors V and VIII. Whilst antithrombin and protein C are unchanged during pregnancy, protein S falls by up to 50% early in the second trimester, limiting the action of both activated protein C and tissue factor pathway inhibitor (TFPI).