

OBSTETRICS

— the physiological changes

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The first article in this month's special feature discusses the physiological changes that take place in a woman's body during pregnancy. It explains how maternal adaptation starts soon after conception and affects many organ systems



Most women gain 10–12kg during pregnancy, comprising amniotic fluid, fetus, maternal water as well as placenta (pictured above)

Maternal adaptation to pregnancy starts soon after conception. Each organ system changes at a different rate and likewise recovers at its own pace, some organs never returning to their pre-pregnancy state. To treat pregnant women, it is crucial to understand the entire range of normal maternal adaptation.

Physiological changes in pregnancy will be influenced by various factors including age, past obstetric history, pre-existing medical disorders and environmental factors. A previous normal pregnancy is the factor most likely to ensure complete and normal adaptation in a current pregnancy. First pregnancies are associated with a lower average birth weight than subsequent pregnancies and this suggests less effective physiological adaptation. Even a pregnancy which aborts in the first trimester will promote more effective adaptation in a subsequent pregnancy in that birth weight is higher and incidence of pregnancy-induced hypertension lower.¹ The latter effect is not as strong after a spontaneous loss as after a termination.

Maternal age has an important influence on adaptation. Chromosomally abnormal fetuses are more common as maternal age increases. Spontaneous abortion, still birth, neonatal death and pregnancy-induced hypertension are more common at the

extremes of reproductive age. Fetal number affects the extent of adaptation. Twin pregnancies have 30 per cent more blood volume and quadruplet pregnancies have 50 per cent more blood volume compared with a pregnancy with a single fetus.²

GENERAL EFFECTS

The average total increase in body water during pregnancy is 8.5L, and this is the same for women in a first or subsequent pregnancy. It consists of fetal fluid, amniotic fluid, placental fluid and maternal fluid (that is, intravascular, oedema and connective tissue fluid). Increased connective tissue fluid is associated with the increase in laxity and pain of some joints, such as the symphysis pubis and lower back. A greater increase in body water is more likely to result in the mother becoming oedematous. Oedema is clinically identifiable in 50 per cent of all pregnancies. It is an index of good physiological adaptation because in otherwise normal pregnancies it has been shown to be associated with increased birth weight and reduced infant mortality.³ Generalised tissue swelling also occurs in the cornea and gingival areas, the latter causing haemorrhage with over-vigorous teeth brushing. Sinus symptoms are worsened by the increase in vascularity and tracheal oedema can be problematic for the anaesthetist if intubation is required. Carpal tunnel syndrome is common. It is characterised by pain, numbness, tingling or burning in one or both hands in the area served by the median nerve, and is

caused by compression of the nerve from oedema as it traverses the wrist. Onset is usually late in pregnancy.

The normal weight gain in pregnancy is between 10–12kg. This comprises fetus, placenta, amniotic fluid, maternal body water and fat. The rate of gain should be stable throughout pregnancy. Low weight gain is associated with low birth weight babies. Nausea and vomiting may result in a fall in weight in the first trimester but usually this is quickly made up. Fat deposition accounts for 3.5kg of the weight gain, with fat accumulating in the abdominal wall, upper back, hips and thighs.

Insomnia is common because of increased awareness of fetal movements when at rest, feeling hot because of peripheral vasodilation and also because of nocturia.

Adrenoceptors increase in number and responsiveness — alpha receptors under the influence of oestrogen and beta receptors under the influence of progesterone,⁴ especially in the uterus. The fetoplacental unit produces renin, placental lactogen, oestrogens and progesterone, which pass into the maternal circulation. Hormone binding varies in pregnancy. Total globulin increases but albumin level is unchanged. Thyroxine binding globulin increases because of increased hepatic synthesis. Plasma aldosterone increases rapidly: by the second trimester, levels are three to five times non-pregnant levels, and by 36 weeks, eight to 10 times. This counteracts the increased progesterone from the placenta plus the increased glomerular filtration rate of pregnancy, both

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of which promote sodium loss and potassium retention. Progesterone and oestrogen increase plasma renin and so the renin-angiotensin-aldosterone system is activated and balances the sodium-losing volume reducing effect. Plasma angiotensin II increases to twice its non-pregnant level by two weeks post conception.⁵ This active pressor agent is antagonised by prostaglandin E2 and prostacyclin⁶ which vasodilate and prevent platelet aggregation. This balance maintains blood pressure at the lower end of the normal range.

Endothelium-derived nitric oxide has been reported to be a vasodilator and to suppress vasoactive substances.⁷ The mid-trimester drop in blood pressure (see below) could be accounted for by increased production of nitric oxide in the arterial circulation of pregnant women.⁸

— CARDIOVASCULAR

Cardiac output is increased by 1.5 L/min to 6.5–7 L/min in the first 10 weeks of pregnancy and remains at that level until term.⁹ It does not return to normal until 12–24 weeks after delivery. Maternal pulse increases by about 15 beats per minute and stroke volume by about 10 per cent — these changes occur continuously throughout pregnancy.¹⁰

In labour, cardiac output rises by 30 per cent during each contraction, with a rise in stroke volume but not a rise in heart rate. Blood expressed by the uterus at each contraction accounts for the rise in cardiac output. Active pushing in the second stage of labour raises both cardiac output and blood pressure even higher. Normotensive women cope with these changes, but the general condition of mothers with cardiac disease or hypertension can deteriorate suddenly or progressively as a result of the changes.

Following delivery, there is an immediate rise in cardiac output as a result of the relief of inferior vena cava obstruction and uterine contraction emptying blood into the systemic circulation. Transfer of fluid from the extravascular space further increases venous return and stroke volume. Women with cardiovascular compromise are therefore most at risk of pulmonary oedema during the second stage of labour and immediately following delivery.

Early or mid-systolic functional murmurs develop in the majority of women by the mid trimester and disappear by a few days after delivery. They can be difficult to differentiate on auscultation from those due to significant cardiac or vascular diseases. Some murmurs arise from the mammary vessels and others are functional, caused by the increase in blood flow, alteration in the configuration of the heart and the physiological haemodilution which occurs in pregnancy.

An apparent haemodilution occurs because of the 50 per cent increase in plasma

volume. There is no decrease in total circulating haemoglobin; in fact, the red cell mass increases by 18 per cent in women not given supplementary iron and by 30 per cent in women given iron. The plasma volume increase is greater in multiple than single pregnancies and greater in subsequent pregnancies than first-time pregnancies. The physiological advantage of increasing plasma is to compensate for the increased blood flow to the uterus and to reduce blood viscosity. A degree of anaemia is therefore a sign of good physiological adaptation.

There is increased blood flow to the periphery, uterus and kidneys. Peripheral vasodilation occurs, causing an increase in temperature of the hands and feet. Uterine and renal blood flow also increases but flow to the liver and brain does not increase.

Blood pressure is directly proportional to cardiac output and systemic vascular resistance. Blood pressure does not rise in normal pregnancy, in spite of the increase in cardiac output, because of peripheral vasodilation. Systolic blood pressure remains constant but diastolic pressure falls during the first and early second trimesters, reaching a plateau at 22 weeks, with a mean fall of 15mmHg. After that, blood pressure rises slowly towards term to reach its pre-pregnancy level.¹¹

A considerable number of previously normotensive women become transiently hypertensive following delivery, due to the return of normal vascular tone. Supine positioning in later pregnancy leads to compression of the inferior vena cava by the uterus which will reduce venous return to the right side of the heart and thus result in a fall in blood pressure. It is important that pregnant women are nursed in the left or right lateral position wherever possible. Most women exhibit a reduction in blood pressure but no actual supine hypotensive syndrome because of collateral circulation. This “aorto-caval” effect is lessened once the fetal head has engaged in the pelvis. It is important that a standardised technique is used to produce clinically useful information regarding blood pressure in pregnancy. The blood pressure must be measured in a relaxed sitting or semi-recumbent woman, using the correct size of cuff at the level of the left atrium. The phase V Korotkoff sound (that is, “disappearance”) should be used because it correlates more accurately with diastolic blood pressure.

Uterine vessels alter in pregnancy. The uterine arteries dilate to 1.5 times their non-pregnant diameter, their arterioles increase three times and the spiral arteries supplying the placenta increase 30 times. Preconception, spiral arteries lie in the myometrium and basal layers of the endometrium. They are muscular and respond to vasoactive stimuli. In normal pregnancies, the spiral arteries are invaded by trophoblastic tissue, dilate and lose the

vasoactive response. This occurs in two waves: at 10–16 weeks and then at 16–22 weeks. In pregnancies associated with pre-eclampsia and intrauterine growth restriction the second invasion wave, into the myometrial portion of the spiral arterioles, fails to occur. The result is that the vessels retain their vasoactive ability and reduce bloodflow to the intervillous space.

Hypertension is the commonest medical problem encountered in pregnancy, affecting 10–15 per cent of all pregnancies. Some women may have been diagnosed hypertensive before the onset of pregnancy. Pregnancy-induced hypertension (raised blood pressure without proteinuria) and pre-eclampsia appear by the second half of pregnancy and generally disappear by six weeks after birth. Pre-eclampsia is a pregnancy-specific multi-system disorder in which diffuse vascular endothelial dysfunction can cause widespread circulatory dysfunction involving the renal, hepatic, cardiovascular, central nervous and coagulation systems.

The venous system becomes more distensible as pregnancy progresses. The predisposition of pregnant women to varicose veins of the legs, vulva, rectum and pelvis is partly due to their distensibility and also to mechanical obstruction of venous return by uterine pressure on the inferior vena cava and iliac veins.

— RESPIRATORY SYSTEM

Due to an increase in metabolic rate there is an increased demand for oxygen in normal pregnancy. There is a 40–50 per cent increase in the minute ventilation, mostly due to an increase in tidal volume rather than the respiratory rate. To allow effective gaseous exchange across the placenta the maternal pCO₂ must be lower than the fetal pCO₂ and so the maternal respiratory centre is reset, probably as an effect of progesterone. A 1mmHg rise in maternal pCO₂ produces a 6L/min increase in ventilation as compared with 1.5L/min, which would occur in the non-pregnant state. The bottom four ribs flare and the diaphragm is raised by 4cm and thus the mechanics of breathing are altered — diaphragmatic movement is increased and costal breathing reduced. This thoracic change causes rotation of the heart and an alteration of the electrocardiogram signal. Tidal volume increases by 200ml and vital capacity by 200ml, and therefore less air is left in the lungs at the end of expiration. Maternal pCO₂ is 4 kPa while fetal pCO₂ is 6kPa and the CO₂ gradient remains beneficial for the fetus.

— GENITAL TRACT

The uterus consists of smooth muscle bundles. Preconception, the uterus weighs 100g and measures 10 × 5 × 2.5cm

but by term it weighs 1,100g and fills almost the entire abdominal cavity. The individual muscle fibres increase in length. The connective, elastic and other tissues also increase in size. The cervix contains only 10 per cent of the uterine muscle fibres, which explains the fundal dominance of contractions.¹² The myometrium functions as a syncytium (a mass of protoplasm with multiple nuclei formed by merging cells, where all the cells act in unison). The uterus contracts spontaneously from 20 weeks gestation, which allows the lower uterine segment to form from the gradual thinning and shortening of the cervix. The endocervical glandular epithelium proliferates and extends out over the ectocervix producing an appearance called "ectropion", which is also seen in women taking combined oral contraceptives. The mucus-secreting nature of this tissue contributes to the increase in clear or white vaginal discharge experienced by pregnant women. The secretions within the

cervical canal produce an antibacterial mucus plug.

The cervix shape changes from cylindrical to conical during pregnancy.¹³ It should remain closed and firm until the fetus has grown and matured. Towards the end of pregnancy the cervix alters its collagen network — the amount of collagen reduces and that of glycosaminoglycans and water increases.¹⁴ This allows cervical ripening to take place.

The cervix contains some PGF_{2a} and more PGE_2 receptors. PGE_2 is produced by the cervix itself as well as the decidua and fetal membranes and it has a physiological role in cervical ripening by breaking down proteoglycan complexes and thus causing degradation of collagen. This is brought about by an increase in collagenase activity.¹⁵

Progesterone inhibits collagenase activity and cervical ripening, hence the effectiveness of the antiprogesterone mifepristone in cervical preparation.¹⁶ During pregnancy, the vaginal epithelium hypertrophies and

the quantity of glycogen-containing cells shed into the vagina increases. Doderlein's bacilli convert the glycogen to lactic acid, producing a pH of 4.0-5.0, discouraging the growth of most pathogens, but not yeasts, which thrive in this environment, predisposing pregnant women to vaginal candidiasis.

— ENDOCRINE

The fetoplacental unit produces human placental lactogen, human chorionic gonadotrophin and other unique hormones. The placenta also contains steroid metabolic pathways. The increase in oestrogen during pregnancy produces an increase in globulins, which bind thyroxine, corticosteroids and sex steroids, increasing total plasma levels but not levels of the free active compound, which remain unchanged. Increased progesterone produces tiredness and sometimes depression but many women are euphoric because of increased levels of corticosteroids.

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The pituitary gland The pituitary increases in size by 30 per cent in a first pregnancy and by 50 per cent in subsequent pregnancies. This can cause headache and increases the likelihood of haemorrhage. This is of particular concern in the anterior pituitary, which has no direct blood supply but receives blood via a portal system from the hypothalamus,¹⁷ – it therefore risks hypoxic damage due to hypotension. Prolactin levels increase by up to 10 fold during pregnancy, returning to normal two weeks after birth, unless the woman breastfeeds. Luteinising hormone and follicle stimulating hormone are both suppressed by the high oestrogen and progesterone levels found in pregnancy. Levels of adrenocorticotrophic hormone (ACTH) and growth hormone produced by the pituitary are unchanged, but the placenta produces ACTH and a specific placental growth hormone and .

Adrenal gland Maternal adrenal glands do not increase in size but the zona fasciculata

Panel 1: Modified Bishop's score ²²				
	0	1	2	3
Dilation (cm)	<1	1–2	2–4	>4
Length (cm)	>4	2–4	1–2	<1
Consistency	Firm	Average	Soft	
Position	Posterior	Mid	Anterior	
Level (presenting part)	Ischial spines –3	–2	–1, at spines	

Clinical assessment of cervical state aids decision making and monitoring in induction of labour. A high Bishop's score indicates spontaneous labour is imminent and response to induction is predicted to be good, while a low score indicates an unripe cervix and may suggest difficulties. (Ischial spines are bony projections of the ischium bone of the pelvis which point inwards and can be felt on vaginal examination to aid assessment of fetal head descent during labour)

increases in width and may have increased secretion. Plasma cortisol and other corticosteroids increase from 12 weeks to term, reaching approximately four times non-pregnant levels. Also, the half-life of cortisol is prolonged and its metabolic clearance is reduced but the level of free cortisol is unal-

tered because the rise in progesterone fills 10 per cent of its binding sites. Levels of angiotensin II and plasma renin activity are increased two to four fold.

Thyroid gland The thyroid increases in size during pregnancy — sometimes resulting in

a frank goitre — as a result of increased blood flow and follicular hyperplasia. Thyroid clearance of plasma iodide is increased because plasma levels fall. This is due to maternal iodine requirements increasing because of active transport to the fetoplacental unit and increased urinary excretion because of the increased glomerular filtration rate and decreased renal tubular reabsorption. Thyroid binding globulin levels double in pregnancy but other binding globulins do not increase. Total thyroxine (T4) and iodothyronine (T3) are increased, resulting in relatively low levels of free T3 and T4 levels, and so the mother remains euthyroid. Serum levels of thyroid stimulating hormone (TSH) fall in the first trimester as the concentration of the structurally similar human chorionic gonadotrophin (hCG) rises. Hyperemesis gravidarum is sometimes associated with high free T4 levels and suppressed TSH. In the third trimester, TSH level rise and free T3 and T4 levels fall.

Parathyroid glands Pregnancy and lactation are associated with increased calcium demands and there is an increased loss of urinary calcium in pregnancy. These factors necessitate a two-fold increase in vitamin D mediated gut absorption of calcium. Parathormone (PTH) is reduced in pregnancy but PTH-related peptide is produced

by the placenta and has a compensatory role in maintaining calcium balance.^{18,19}

Pancreas The islet of Langerhans cells increase in size and the beta cells and the insulin receptor sites increase in number. Serum insulin levels are higher in the second half of pregnancy and response to glucose load is greater than in the non-pregnant state but the fall in blood sugar is less. Therefore, fasting glucose levels are decreased but levels following a meal are increased compared with the non-pregnant state. There is relative resistance to insulin due to increased levels of human placental lactogen, prolactin, cortisol and other insulin antagonists. As pregnancy advances, the resistance increases. Pregnancy is a state of insulin resistance and glucose intolerance. Pregnant women double their insulin production and women with insulin-dependent diabetes have increased insulin requirements. The renal threshold for glucose falls and many women will have glycosuria at some point in pregnancy. The prevalence of gestational diabetes depends on ethnicity and the criteria used for serum glucose testing.

— BLOOD CELLS

The circulating mass increases by 20–30 per cent in pregnancy as a result of increase in the number and size of the red

cell and also an increase in the reticulocyte count. This may be due to the fall in the oncotic pressure of plasma or to the release of immature cells from the hyperplastic marrow. Also contributing is the rise in erythropoietin from as early as 16 weeks.²⁰

Iron is incorporated into pregnant women more readily. With the 10 or more suppressed menstrual cycles approximately 250mg of iron is saved but 550mg is needed for the placenta and fetus and the same for the mother, so the marrow has to respond actively to compensate. There is no uniform response by white cells but generally neutrophil numbers rise until 30 weeks and may reach $20 \times 10^9/L$. Platelets levels tend to fall but remain above $200 \times 10^9/L$ in normal pregnancy.

— THROMBOEMBOLIC DISEASE

Changes in pregnancy produce a hypercoagulable state, presumably to stop bleeding after delivery. The concentrations of certain clotting factors, particularly VIII, IX and X, are increased. Fibrinogen levels rise by up to 50 per cent and fibrinolytic activity decreases. The concentration of endogenous anticoagulants, such as antithrombin III and protein S, falls. Pregnancy alters the coagulation system in favour of venous thromboembolism and this risk persists for at least six weeks after birth. Venous stasis occurs

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in the lower limbs as a result of venodilation and obstruction to venous return caused by the abdominal mass. This can result in thrombosis and thromboembolism — the leading cause of maternal death in the UK.²¹

RENAL

An increased frequency of micturition is common from the first trimester and nocturia is almost inevitable later, aggravated by polydipsia by day, and return of oedema to the general circulation when recumbent. Stress incontinence is common, due to relaxation of bladder supports and an increased intra-abdominal pressure. The detrusor muscle and ureters relax, but reflux is uncommon because of the proliferation of Waldeyer's sheath around the ureter where it passes through the bladder wall. Dilation of the ureters occurs in 90 per cent of women, more commonly on the right, and can occur as early as six weeks gestation due to hormonal

effects and uterine size compressing the lower ureter. This, in turn, causes an increase in renal size due to increased glomerular size.

Renal plasma flow increases by 50 per cent and the glomerular filtration rate by 60 per cent above non-pregnant levels by the 16th week of pregnancy.² This is related partly to the increased cardiac output and, later, to decreased resistance of the efferent glomerular arteriole. Reduced oncotic pressure also contributes. The tubules are thus presented with increased quantities of urine and also lose some of their reabsorptive capacity, which results in some substances, such as glucose and amino acids, being less well resorbed than in the non-pregnant woman. Protein loss is increased by up to 300mg per 24-hour period.

Renal handling of water is largely unchanged in pregnancy, but water retention often occurs due to changes in renal retention of sodium. Progesterone increases sodium excretion, and aldosterone, mineralocorticoids and prostaglandins also affect body sodium.

GASTROINTESTINAL

Taste often alters in pregnancy. Gastric secretion is reduced and delayed emptying is a problem, especially in labour because some analgesic agents exacerbate this, placing the patient at risk of regurgitation and aspiration — Mendelson's syndrome.

Heartburn is common in pregnancy, producing pain from stomach acid refluxing due to an increase in gastric pressure and relaxation of the gastro-oesophageal sphincter. The whole gut has reduced motility, which may contribute to increased water and salt loss and to constipation.

Nausea and vomiting are common, affecting 50 per cent of women. Hyperemesis gravidarum is severe or protracted vomiting sufficient to cause fluid, electrolyte and nutritional disturbances. It affects only 0.1–1 per cent of pregnant women. It may be related to the levels of hCG acting as a thyroid stimulator.

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Some hepatic functions are affected by pregnancy. For example, albumin concentration falls but albumin binding capacity is not affected, because the total amount circulating is unchanged. Alkaline phosphatase levels rise, largely due to increased placental production.

Cholestasis almost always occurs in pregnancy. There is stasis of bile in dilated biliary canaliculi which can produce generalised pruritus. This responds to cholestyramine; it may recur in subsequent pregnancies or if the woman takes combined oral contraceptives. Maternal handling of many drugs is altered as renal clearance is speeded up and reduces the effective dose.

— SKIN

There are some areas of change in skin pigmentation during pregnancy — development of the linea nigra (a dark line down the abdomen), nipple and areolar

darkening and facial chloasma. All are due to increased melanocyte stimulating hormone. Oestrogen produces reddening of the palms and spider naevi.

Increased corticosteroids cause striae gravidarum on the abdomen, breasts and elsewhere. Pruritus without rash or obstetric cholestasis can be a feature of a normal pregnancy.

— LABOUR AND DELIVERY

Normal term labour occurs after 36 completed weeks of pregnancy. The onset of labour can be difficult to diagnose but is defined as regular, painful, uterine contractions associated with cervical thinning and dilation. Labour is divided into three stages. The first stage is from onset to full cervical dilation and is further divided into the unpredictably long latent phase (up to approximately 3cm dilatation) and the active phase (when dilatation occurs at

around 0.5–1cm per hour). In practice, labour is timed from admission to the labour suite or when objective assessment of the cervix can be made by digital vaginal examination. The second stage is from full dilation to delivery of the baby and again can be divided into the passive and active (pushing) stages. The third stage of labour is from delivery of the baby until the placenta has been delivered.

Pain in labour is caused by ischaemia of the myometrium during the contraction due to obliteration of the arterioles serving the muscle. There is great variation in how women perceive the pain of labour and therefore in analgesic requirements. The pain of childbirth is different from other types of pain in that there is an achievable end product of having a baby and it may therefore be amenable to many types of “alternative” pain relief such as relaxation techniques and use of the birthing pool, as well as more traditional analgesia.

The mode of delivery for the majority of women is still spontaneous delivery but the caesarean section rate is rising. Depending on the type of hospital this rate may be as high as 23 per cent. Caesarean sections may be elective (such as for breech presentation), emergency (for fetal distress or failure to progress) and semi-elective (for an indication such as severe intra-uterine growth retardation). Approximately 10 per cent of deliveries are "operative vaginal" – they require use of a ventouse (suction cap) or forceps.

Induction of labour is performed for a variety of indications but most commonly for post maturity between 41 and 43 weeks gestation. The mode and success of induction will depend on the degree of cervical ripening as determined by a vaginal examination. To assess cervical ripeness the Modified Bishop's score is useful²² (see Panel 1).

■ AFTER DELIVERY

Maternal metabolism may not return to the pre-pregnancy state. Striae and pigmentation become less obvious but persist. Weight often stays 1kg above preconception, especially if the mother does not breastfeed. Uterine vascularisation is permanently increased so periods are often heavier.

However, other systems do return to normal. Carbohydrate metabolism is normal by 24 hours after birth. Cardiac output is normal by two weeks after birth but cervical ectropion may persist for one year.

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