Practical & Obstetrics & Gynaecology

2nd edition

Department of Obstetrics and Gynaecology
School of Clinical Medicine
The University of Hong Kong

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Second Edition

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HKU Med School of Clinical Medicine
Department of Obstetrics & Gynaecology
香港大學婦產科學系

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Preface from Chief Editor, Professor Pak-chung Ho

This is an undergraduate textbook in Obstetrics and Gynaecology. In the past, because of historical reasons, medical students in Hong Kong mainly used the British Obstetrics and Gynaecology textbooks. While there are many good British textbooks, there is still a need for a local textbook for the undergraduate as the epidemiology of various diseases in our local population (mainly Southern Chinese) is different from those in Britain. Moreover, the health care system and the laws and regulations governing medical practice are also different. This book was written to fill this gap.

As the main target audience for this book are the undergraduate medical students, we provide a comprehensive coverage of all the topics in the core curriculum of Obstetrics and Gynaecology for medical undergraduates. In addition to the description of the various diseases, there is also discussion on the evidence-based approach to the differential diagnosis and management of common symptoms/presentations in Obstetrics and Gynaecology. When appropriate, flow charts and diagrams are used to help the readers to make a diagnosis. This book also contains more information on diseases more common in this region. Although this book was mainly written for medical students, this textbook will also be a useful basic reference for the student midwives, practising doctors as well as other health care professionals involved in women's health care.

Health care is an ever-changing landscape, which knowledge and practice should be reviewed and updated regularly. The Department of Obstetrics and Gynaecology of University of Hong Kong has decided that the publication of this book should be a project of the Department which would undertake the responsibility of regular updating of this book. Therefore, we now publish the second edition. Finally, I would like to thank all the authors for their contribution to the writing of the various chapters, the section editors for the planning, co-ordination and editing the different sections, and Dr. Vincent Cheung and Dr. Jennifer Ko for the final formatting and making arrangement for the printing of the book.

Professor Pak-chung Ho

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Preface from Deputy Chief Editor, Professor Hextan Y.S. Ngan

The Department of Obstetrics and Gynaecology is happy to produce a simple and practical textbook for easy reference to undergraduates. It is anticipated that with the change in teaching and learning, more emphasis would be web based. The change is also because new knowledge and findings come quicker in this modern era of medical and scientific development. Thus, this text book serves as a foundation or starting point where basic and practical knowledge and skills in obstetrics and gynaecology are presented in a simple and easy to read format to help readers to get the key points to build on new knowledge and skills as time goes. However, it is our duty to update this book periodically so as to remove outdated practice and endorse new developments where every primary practitioner should know in the area of obstetrics and gynaecology. This is important as specialists in obstetrics and gynaecology, we would be able to consolidate essential findings from a sea of web based information that one may get loss of which is the key information.

I would like to thank Professor PC Ho and team who make great effort to make this textbook of particular relevance to Hong Kong.

Professor Hextan Y.S. Ngan

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Chapter 1

Anatomy of the Female Pelvis

Charleen S.Y. Cheung

External Genitalia

1. The vulva is bounded anteriorly by the mons pubis, laterally by labia majora, and posterior fourchette.

2. The labia minora consist of connective tissue folds devoid of hair follicles. They fuse anteriorly to form the prepuce of clitoris and frenulum beneath, and posteriorly the fourchette.

3. The perineum is the base of perineal body, from fourchette to anus.

4. Hymen is the mucosal entrance to vagina.

5. The vestibule includes opening to vagina and urethra. It is the area between the introitus and the Hart line, where non-keratinised squamous epithelium meets keratinized squamous epithelium of labia minora.

6. Various glands are located in this area to produce secretions for lubrication: major vestibular (Bartholin's) gland is located at posterior one third; paraurethral (Skene's) glands near external urethral meatus.

Pelvic Organs (Figure 1.1)

1. Vagina is approximately 8 cm from introitus to cervix, longer posteriorly and wider proximally. It is a distensible canal consisting of an outer and an inner circular muscle layer, lined with stratified squamous epithelium. It has no glands. Its anterior and posterior walls oppose each other in usual position. It has acidic environment (pH around 4.5) due to breakdown of glycogen by normal commensals (Doderlein's bacilli) in premenopausal women.

2. Uterus is approximately 7.5cm long, 5cm wide, 3 cm thick. The adult uterus weighs about 70 g. It is heavier in multiparous women. It is a pear shaped organ with thick muscular wall and a central cavity. It consists of three layers: outer serosal layer (peritoneum), middle muscular layer (myometrium) and inner mucous layer (endometrium). It consists of superior fundus, cornu, main body, isthmus (anatomical constriction at internal os and histological internal os where mucous membrane becomes columnar epithelium of the cervix), and cervix (supravaginal and vaginal portions). The longitudinal axis of uterus is approximately at right angle to vagina, usually in anteversion (while 20% are retroverted). The uterus is suspended in position by round ligament, broad ligament, suspensory and ovarian ligaments; and by pelvic floor and three connective tissues: pubocervical ligaments anteriorly, cardinal ligaments laterally, and uterosacral ligaments posteriorly. Pouch of Douglas is covered by peritoneum posteriorly.

3. Cervix is the lower fibromuscular portion of uterus. It measures 3-4 cm long and 2.5 cm wide. It varies in shape and size depending on age, parity and menstrual phase: the corpus grows faster and lengthens with estrogenic effect at puberty; while the cervix becomes more atrophic and becomes flushed with vaginal vault after menopause. The ectocervix is readily visible, covered by pink stratified squamous epithelium with multiple layers of cells. The endocervix is not visible as it lies proximal to external os, lined by a reddish, single layer of columnar cells, which secretes an alkaline mucus neutralizing the effect of vaginal acidity. The location of squamous columnar junction in relation to external os changes with age and estrogen status. Squamous metaplasia refers to the physiological replacement of the everted columnar epithelium on the ectocervix by a newly formed squamous epithelium from the subcolumnar reserve cells. The transformation zone refers to the region of cervix where squamous metaplasia occurs, it is of clinical importance in colposcopy, as most cervical intraepithelial neoplasia and carcinogenesis occur here. Parametrium refers to the connective tissue anterior and lateral to supravaginal portion of cervix.

4. Ovary is an almond-shaped organ, approximately 3 cm x 2 cm x 1 cm in size. Its appearance varies with age and stage of the menstrual cycle. It is the only intra-abdominal structure not covered by peritoneum. It consists of a central vascular medulla and an outer denser fibrous cortex. Each ovary is attached to the broad ligament posteriorly by mesovarum, medially to the uterus by the ovarian ligament,

and the infundibulopelvic ligament which carries blood supply directly from aorta.

5. Fallopian tube is a 10 cm tubular structure that extends from uterine cornu to end near the ovary on each side. It runs in the upper margin of the broad ligament (mesosalpinx). It is divided into four parts: most medial interstitial portion is embedded into uterine wall, isthmus next is the narrowest portion, followed by ampulla the longest and widest portion, before it ends into most laterally a funnel shaped infundibulum with fimbrial ends and projections lie over the ovary. The inner surface of fimbria and fallopian tube is lined by ciliated epithelium, its motion helps to propel the fertilized ovum to the uterine cavity.

6. Urinary bladder is located behind the pubic bone and anterior to uterine cervix and upper vagina. It is a highly compliant organ with strong muscular wall made up of detrusor muscles running in different directions and lined by urothelial mucosa. The trigone is the area where mucosa is closely adherent to muscles. The ureteric openings mark its superior margin, while urethra lies inferiorly.

7. Urethra measures around 4 cm in female. It lies behind the pubic symphysis and embedded in anterior vaginal wall. It is lined by squamous epithelium near external meatus, and transitional in upper two thirds. The muscles at internal meatus act as sphincter while pelvic floor muscles act as external voluntary sphincter for control of urine flow.

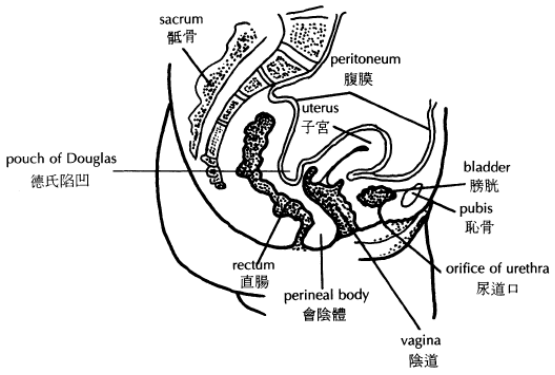
8. Ureter measures about 25-20 cm in adult. It runs abdominally from renal pelvis to trigone: anterior to the surface of psoas major retroperitoneally, enters pelvic cavity by crossing pelvic brim at sacroiliac joint, anterior to bifurcation of iliac artery, courses along lateral pelvic sidewall, posterior to ovary and deep into broad ligament; it passes under the uterine artery ("water under the bridge"), before turning anteriomedially at level of ischial spine, into bladder transversely via cardinal ligament. The most common sites of ureteric injuries in gynaecological surgeries are (i) lateral to the uterine vessels, (ii) area of the uterovesicle junction close to the cardinal ligaments, (iii) the base of the infundibulopelvic ligament as the ureters cross the pelvic brim at the ovarian fossa and (iv) at the level of the uterosacral ligament. Clear understanding of the course of ureter is important in preventing its injury in pelvic surgery, particularly in hysterectomy, oophorectomy or with presence of dense adhesions.

9. Rectum starts at level of S3 as continuation of sigmoid and measures about 12 cm long. The anal opening is about 2.5 cm behind vaginal orifice. The puborectalis muscle forms a sling at the junction with anal canal. Faecal incontinence occurs when anal sphincters are torn in traumatic vaginal deliveries.

Figure. 1.1. A. Sagittal view of female pelvic organs; B. Female internal genital organs.

(Figures adapted from Practical Obstetrics: A Short Textbook in English and Chinese for Students and Midwives, by Daphne W.C. Chun and K.H. Lee, with permission from Prof. K.H. Lee.)

A



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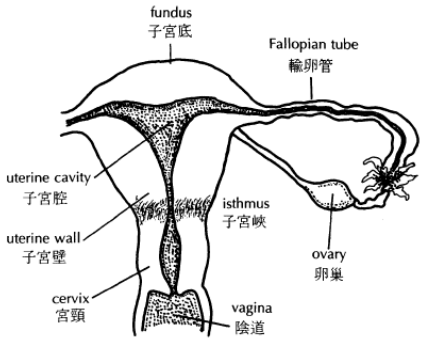


Pelvic Floor

1. It serves two key functions: physiological support to pelvic viscera, and constrictor in continence mechanism.

2. Pelvic diaphragm extends from symphysis pubis to the coccyx between sidewalls, forming the inferior border of abdominopelvic cavity.

3. Urogenital diaphragm (the triangle ligament) is external and inferior to the pelvic diaphragm.

4. Superficial layer consists of external anal sphincter, perineal body and transverse perinei.

5. Deep layer consists of the pubococcygeus, iliococcygeus, coccygeus (constitute the levator ani); and puborectalis (which in fact lies between superficial and deep layers).

Bony Pelvis (Figure 1.2)

1. It is composed of pubis, sacrum, ilium and ischium.

2. Pelvic inlet is the plane marked by sacral promontory and superior aspect of symphysis pubis.

3. Mid cavity describes the curved canal between inlet and outlet, curving downward and backward first, then forward along the wall of sacrum posteriorly.

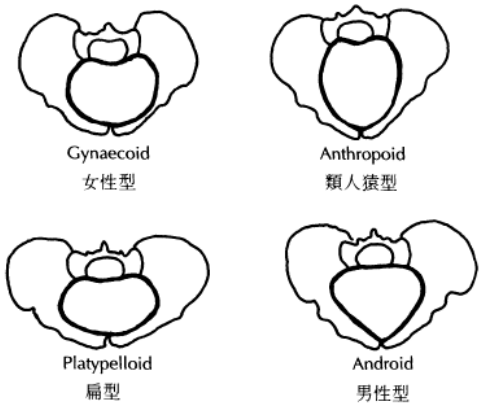
4. Pelvic outlet is located at tip of coccyx to inferior rami and lower border of symphysis pubis.

5. There are generally four different shapes of female pelvis
   - Gynaecocoid – roundish, normal female pelvis, suitable for childbirth
   - Anthropoid – anterioposterior > transverse diameter
   - Platypelloid – transverse > anterioposterior diameter
   - Android – resembles male pelvis, most unfavourable for childbirth
   - Mixed form of pelvis is not uncommon.

6. In a series of about 1,000 Chinese women, 80% were of gynaecocoid type, 13.6% were anthropoid, <1% were android. When compared to American data, gynaecocoid pelvis was twice as common as in Chinese, android pelvis was rare in Chinese. Chinese women are on average shorter in height than Caucasian women. However, their pelvic measurements were comparable. Given more favourable pelvic shape and size, as well as smaller average size of the babies at term, Chinese women have relatively easier labour.

Figure 1.2. Basic types of bony pelvis.

(Figure adapted from Practical Obstetrics: A Short Textbook in English and Chinese for Students and Midwives, by Daphne W.C. Chun and K.H. Lee, with permission from Prof. K.H. Lee.)



Blood Supply

1. Abdominal aorta branches into right and left common iliac artery at L4 level.

2. External iliac artery leaves abdominal cavity → supplies lower extremities

3. Internal iliac artery supplies pelvic organs, gluteus and perineum
   - Anterior division:
     - umbilical, superior vesical
       → superior aspect of bladder
     - obturator
       → pelvic muscles, ilium, femoral head, medial thigh
     - uterine
       → uterus and vagina
     - internal pudendal
       → inferior rectal
       → perineal
       → posterior labial
       → vestibules of vagina
       → deep and dorsalartery of clitoris
     - inferior gluteal
       → levator ani, coccygeus, piriformis, quadratus femoris, upper posterior thigh, gluteus maximus, sciatic nerve
     - middle rectal.
   - Posterior division:
     - iliolumbar
     - lateral sacral
     - superior gluteal.

4. Other arterial supplies to pelvis
   - Ovarian (arising from aorta at L1 level below renal arteries)
   - Inferior mesenteric
     → superior rectal (anastomose with middle and inferior rectal)
   - Middle sacral.

5. Venous return: external and internal iliac, middle sacral veins.
   - accompanying arteries of the same name
   - they form plexus around the organs and form anastomoses, explaining why pelvic infections spread easily
   - ovarian vein drains to inferior vena cava on the right, and left renal vein on the left
   - left renal vein is smaller and more prone to obstruction, thus pelvic varicosities are more common on left side

Lymphatic Supply

There are extensive interconnections in the pelvis
- superficial and deep inguinal: inferolateral part of trunk and perineum
- external iliac nodes: from inguinal
- internal iliac nodes: pelvic organs, glueal, perineal regions
- sacral nodes: drain into internal or common iliac nodes
- common iliac nodes: from pelvic viscera
- lumbar nodes: from above, associated with aorta and inferior vena cava
- infection or malignancy of pelvic organs spreads along the respective lymphatic drainage.

Nerve Supply

1. Sacral plexus (L4-S4)
   - Sciatic nerve (L4-S3) gives rise to articular branches to supply hip joint and muscular branches to flexors of knee in thigh and all muscles in leg and foot
   - Pudendal nerve (S2-4) is the main nerve in the perineum. It carries sensory nerves from the genitalia, motor supplies to the perineal muscles, external urethral sphincter, and external anal sphincter
   - Superior (L4-S1) and inferior (L5-S2) gluteal nerves
   - Muscular branches include quadratus femoris (L4-S1), obturator internus (L5-S2), pirifomis (S1-2), levator ani and coccygeus (S3-4)
   - Perforating cutaneous and posterior femoral cutaneous
   - Pelvic splanchnic nerves (S2-4).

2. Lumbar plexus (L1-5)
   - Ilioinguinal, labial branch to labia majora
   - Genitofemoral, genital branch to labia majora.

3. Coccygeal plexus (S4-5), coccygeal, anococcygeal.

4. Sympathetic innervation consists of lumbar splanchnic nerves, sacral splanchnic nerves, superior hypogastric, inferior hypogastriac (mixed parasympathetic) and peri-arterial plexuses.

5. Parasympathetic innervation involves the pelvic splanchnic nerves, inferior hypogastric plexus (urethra, rectum), and uterovaginal plexus (uterus, vagina, ovaries).

Key Points

- Understand the anatomy of the external genitalia, pelvic organs in relation to their clinical significance.
- Understand the pelvic floor, various shapes of bony pelvis and their implications in labour.
- Understand the course of the ureter and the common sites of injury in gynaecological surgery.
- Understand the major blood, lymphatic and nerve supplies to the pelvis.

Suggested Readings

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Fortner, Szymanski, Fox, Wallach. The John Hopkins Manual of Gynecology and Obstetrics. Published by Lippincott Williams & Wilkins. 2007. Third Edition.

Terms with Chinese Translation

Bartholin's gland - 前庭腺
clitoris - 陰蒂
coccygeal plexus - 尾椎神經叢
ectocervix - 外子宮頸
endoocervix - 內子宮頸
fallopian tube - 輸卵管
  ampulla - 壺腹部
  fimbrial end - 傘端
  infundibulum - 漏斗部
  interstitial portion - 間質部
  isthmic portion - 峽部
hymen - 處女膜
iliac artery - 髂動脈
infundibulopelvic ligament - 骨盆漏斗韌帶
mesenteric artery - 腸系膜動脈
parametrium - 宮旁
parasympathetic nerve - 副交感神經
pelvic floor - 盆底
pudendal nerve - 陰部神經
rectum - 直腸
sacral plexus - 薦神經叢
sciatic nerve - 坐骨神經
sympathetic nerve - 交感神經
ureter - 輸尿管
urethra - 尿道
urogenital diaphragm - 泌尿生殖隔膜

Chapter 2

Physiology in Pregnancy

Vivian K.S. Ng, Wing-cheong Leung

Introduction

There are numerous significant changes in the body that begin soon after fertilization and occur throughout pregnancy. Some of them may cause discomfort to the women while others may be subtle and may not be noticed. These changes are important to adapt to the physiological stimuli provided by the fetus.

Metabolism

1. Water
   - Increased water retention partly by fall in plasma osmolality.
   - Total body water content increases by 6.5 L (3.5 L from fetus, placenta and amniotic fluid and 3 L from increase in blood volume and size of uterus and breast).
   - Pitting oedema of lower limbs from increased pressure of venous system below gravid uterus.
   - Studies suggested that maternal body water rather than fat correlated more with infant birth weight.

2. Protein
   - Essential for development of fetus, placenta, maternal blood and plasma proteins, uterine muscles and breast glands.
   - Increase dietary protein intake during pregnancy to fulfil the requirement.
   - More efficient use of dietary protein as gestation advances.

3. Carbohydrate
   - Peripheral resistance to insulin increased in normal pregnancy to ensure postprandial hyperglycaemia to supply fetus.
   - Mechanism remains unknown: oestrogen, progesterone and placental lactogen believed to be associated with the insulin resistance.
   - Accelerated starvation (switch of energy source from glucose to lipid) in response to rapid change of status from hyperglycaemia to fasting state.
   - Ketonaemia accelerated in starvation compared with non-pregnant women.
   - Results in mild fasting hypoglycaemia, postprandial hyperglycaemia and hyperinsulinaemia.

4. Fat
   - Plasma concentration of lipids, lipoproteins and apolipoproteins increase in pregnancy.
   - Fat deposition as energy storage increases from mid trimester but drops later as fetal demand increases.
   - Influenced by oestrogen and progesterone
   - Decreases after delivery (decrease accelerated in lactation).

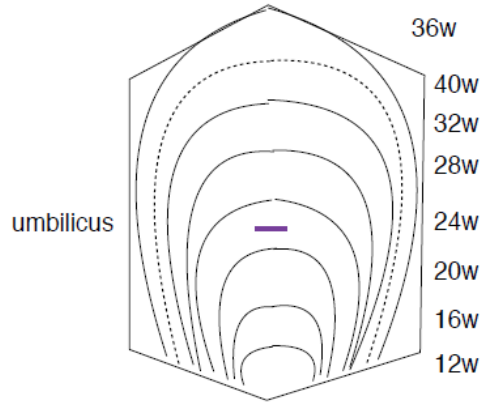
5. Electrolyte and minerals
   - Excretion of potassium and sodium remains unchanged in pregnancy as increased glomerular filtration is compensated by the enhanced reabsorption in renal tubules.
   - Serum concentration of potassium and sodium decrease slightly due to expanded plasma volume.
   - Total serum calcium decreases but the ionised calcium level remains the same.
   - Dietary calcium intake is important as significant amount of maternal calcium is deposited in fetal skeleton.
   - Serum magnesium level declines while phosphate level within non-pregnant state.

Reproductive Tract

1. Uterus
   - Enlarged with increased vascularity, hyperplasia and hypertrophy of muscle cells (Influenced by oestrogen and progesterone in early gestations and pressure exerted by the product of conception later on).
   - Pear shape when conceived; become spherical and palpable above symphysis pubis from 12 weeks onwards; at umbilical level by 22-24 weeks; xiphoid process at term; lightening as fetus engaged.
   - Contraction: Irregular, painless contraction, called Braxton-Hicks contraction may first be felt after first trimester, more frequent and rhythmic as gestation advances.

- Uteroplacental blood flow
  - Increases progressively to 450-650ml/min by vasodilation of maternal vessels and growth of placental vessels
  - Controlled by oestrogen and progesterone
  - More sensitive to catecholamines while refractory to renin-angiotensin effect to vasoconstriction
  - Blood flow decreases during uterine contraction that is proportional to its intensity

Figure 2.1. Uterus size at different gestational ages.



2. Cervix
   - As soon as conception begins, the cervix softens due to increased vascularity and oedema.
   - Hyperplasia and hypertrophy of the cervical glands make squamo-columnar junction everted and appeared red and velvety and more friable with bleeding.
   - Endocervical glands produce copious mucus to fill the cervical canal soon after conception. At onset of labour, this mucus plug, or operculum, is expelled (called show).

3. Ovaries
   - Ovulation and maturation of oocyte suppressed.
   - Corpus luteum produces progestogen to support pregnancy before 7 weeks.
   - Decidual reaction on surface which bleeds easily.

4. Vagina and perineum
   - Vaginal mucosa thickens and increases vascularity resulting in violet-bluish colour.
   - Increase in whitish vaginal discharge due to cervical stimulation by oestrogen and progesterone.
   - pH of vaginal discharge is more acidic (pH 3.5 - 6) due to increased production of lactic acid by Lactobacillus acidophilus.
   - Acidic environment protects against bacterial infection but increases susceptibility to candida infection.
   - Perineum enlarged due to increased vascularity, hypertrophy of connective tissues and fat deposition.

Breasts

1. Fullness and tingling sensation in early gestation as influenced by oestrogen and progesterone.

2. Areolae become hyperpigmented with hypertrophy of sebaceous gland (Montgomery tubercles) that keeps the nipples lubricated during breastfeeding.

3. From second to third trimesters, proliferation of lactiferous ducts and lobule-alevolar tissues stimulated by placental hormones promotes breasts to enlarge.

4. Lactation inhibited until decrease in oestrogen level after birth.

Cardiovascular & Haematological Systems

1. Blood volume
   - Increases by 45% resulting from increase in plasma volume and erythrocytes.
   - To meet the demand of the enlarged uterus.
   - Accommodate for the impaired venous return as a result of the pressure from gravid uterus.
   - Compensate for the blood loss during delivery.

2. Haemoglobin and haematocrit level
   - Decreases because the plasma volume increases more relative to erythrocytes increase (haemodilution).
   - Iron demand increases during pregnancy; anaemia and decrease in haematocrit are common in pregnancy.

3. Stroke volume, heart rate, peripheral vascular resistance and cardiac output
   - Stroke volume increases by 30% by the end of third trimester.
   - Heart rate increases by 15% at first trimester to 25% at the end of second trimester.
   - Peripheral vascular resistance decreases due to progesterone effect on smooth muscles leading to fall in blood pressure in the first 24 weeks of gestation.

- Increase in stroke volume and heart rate and decrease in peripheral vascular resistance give rise to raised cardiac output.
- Cardiac output increases by 30-50% during pregnancy, reaching its peak at 24 weeks; maintains its maximum until 1-2 weeks after delivery.

4. Blood pressure
   - Systolic blood pressure drops mildly by 6-8%.
   - Diastolic blood pressure drops markedly by 20-25% in the first two trimesters followed by gradual rise to non-pregnant level till term.
   - Due to placenta function as arteriovenous shunt, peripheral vasodilating factors, such as oestrogen, progesterone, and increased endothelial synthesis of prostaglandin E2, prostacyclin.

5. ECG changes
   - Sinus tachycardia, atrial and ventricular ectopics.
   - Rotation of axis to the left.
   - ST depression and T wave inversion at lateral and inferior leads.
   - Changes observed in cardiac echo: left ventricular hypertrophy, increase in left ventricular mass by 50% at term, 12% increase in size in aortic, pulmonary and mitral valves.

Gastrointestinal System

1. Increase in appetite and intake.

2. Morning sickness from 4-6 weeks of gestation and usually subsides at the end of first trimester (hyperemesis gravidarum: severe nausea and vomiting with weight loss, dehydration and electrolyte disturbance happens in 1% of pregnancies).

3. Progesterone decreases muscle tone and motility of smooth muscles, resulting in oesophageal regurgitation, delayed gastric emptying and increased water reabsorption in colon and hence constipation.

4. Increase in iron absorption in small intestine to accommodate need in pregnancy.

5. Increase in portal venous pressure, in addition to increased intraabdominal pressure leads to haemorrhoids.

6. Gallbladder distended due to decreased muscle tone. This leads to prolonged retention of bile causing gallstone.

7. Intrahepatic cholestasis in response to placental steroids may result in pruritus gravidarum and possible implications of fetal wellbeing.

Respiratory System

1. Oxygen consumption increases by 40%.

2. Lung Function
   - Tidal volume increases by 30-40%.
   - Minute ventilation increases by 30-40%.
   - Expiratory reserve volume falls by 20%.
   - Residual volume and total lung volume decrease due to elevation of diaphragm.
   - Function residual capacity therefore decreases.
   - Vital capacity, inspiratory reserve volume, respiratory rate remain unchanged.

3. Arterial blood gas
   - pH remains unchanged at 7.4 - 7.45.
   - Respiratory alkalosis results from drop in PCO2 is compensated metabolically by reduction of serum bicarbonate concentration.

Renal System

1. Increased size of kidneys and dilation of ureters, renal pelvis and calyces due to hormones (oestrogen, progesterone), pressure from gravid uterus and increased plasma volume.

2. Increase in glomerular filtration rate and renal plasma flow by 50% resulting in increased creatinine clearance.

3. Reduced tubular reabsorption of glucose and amino acids results in possible glycosuria and proteinuria but the exact mechanism remains unknown.

Endocrine System

1. Pituitary gland & placental hormones
   - Pituitary gland enlarges by 135% in pregnancy but rarely compresses optic chiasma and affect vision.
   - Elevated oestrogen and progesterone produced by the corpus luteum suppress luteinizing hormone and follicular-stimulating hormones. Maturation of follicle and ovulation ceased.
   - Human chorionic gonadotropin produced by the fertilized egg and chorionic villi

supports corpus luteum to function till placenta takes over.
- Progesterone relaxes smooth muscle and therefore reduces uterine contraction and miscarriage.
- Oestrogen relaxes pelvic ligaments and joints and promotes reabsorption of sodium and water from renal tubules.
- Both progesterone and oestrogen promote fat deposition under skin as energy reserve for pregnancy and lactation.
- Prolactin level increases in pregnancy for ten-fold at term and is responsible for initiating lactation.
- Growth hormone secreted from pituitary gland (in first trimester) and placenta (8 weeks onwards) increases till 28 weeks of gestation. It regulates fetal growth and is associated with onset of labour.
- Oxytocin production increases as pregnancy matures and stimulates uterine contraction and let-down reflex. Its action is inhibited by high level of progesterone until term.
- Human chorionic somatomammotropin, formerly named as human placental lactogen, acts as growth hormone and promotes breast development.

2. Thyroid gland
   - Thyroid gland enlarges by glandular hyperplasia and increased vascularity.
   - Thyroxine-binding globulin increases.
   - Rises in total thyroxine (T4) and total triiodothyronine (T3).
   - Relative iodine deficiency status due to increased renal clearance.
   - Total T4 increases since 6-9 weeks and plateaus at 18 weeks.
   - Free T4 and T3 mildly elevated in first trimester and back to non-pregnant level afterwards.
   - Thyroxine-releasing hormone level remains stable in pregnancy. It stimulates fetal pituitary to secrete thyrotropin.
   - Thyroid stimulating hormone and human chorionic gonadotropin (hCG): share the same alpha-subunit of glycoprotein. Hence, hCG has thyrotropic activity.
   - However, these changes do not alter maternal thyroid physiology.

3. Parathyroid glands
   - Slight hyperparathyroidism results from the increased fetal need of calcium and vitamin D.
   - Peak level between 15 and 35 weeks when fetal skeleton growth is greatest.

4. Pancreas
   - Fetus requires significant amount of glucose for its development and growth achieved by consuming maternal glucose.
   - Maternal insulin production decreases in early pregnancy.
   - Oestrogen, progesterone, cortisol and human chorionic somatomammotropin increase maternal resistance to insulin and impair glucose metabolism.

5. Adrenals
   - Increased aldosterone results in increased reabsorption of sodium from renal tubules.
   - Cortisol increases while adrenal corticotropin reduces.

Skin

1. Striae gravidarum due to stretching of the skin over abdomen and sometimes breasts and thighs in later months of pregnancy.

2. Hyperpigmentation observed in linea alba (linea nigra), aerolae, axilla, genital skin is due to melanotropin from pituitary and the melanocyte-stimulating effects from oestrogen and progesterone.

3. Chloasma (facial blotchy brownish hyperpigmentation of skin over cheek, nose and forehead) appear in 50-70% of pregnant women.

4. As a result of hyperestrogenaemia, vascular spiders, tiny star-shaped angioma on neck, thorax, face and arm, and palmar erythema are found.

5. These changes would regress after delivery.

Key Points

- Physiological changes of pregnancy are important in the understanding of common symptoms of pregnancy.
- Investigation results should be interpreted with pregnancy normal ranges if available, instead of the non-pregnant normal ranges.
- Changes are not limited to the genital systems, but affect all the major systems in the body.

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American College of Obstetricians and Gynecologists. Weight gain during pregnancy. Committee Opinion No. 548. Obstet Gynecol 2013;121:210–2

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Royal College of Obstetricians and Gynaecologists. Obstetric cholestasis. Green-top Guideline No. 43. April 2011.

Terms with Chinese Translation

amniotic fluid - 羊水
anaemia - 貧血
areolae - 乳暈
Braxton-Hicks contraction - 無痛宮縮
breasts - 乳房
cervix - 子宮頸
chloasma - 妊斑
cholestasis - 膽汁淤積
chorionic villi - 絨毛膜
constipation - 便秘
haemoglobin - 血紅素
haemorrhoids - 痔瘡
human chorionic gonadotropin - 人絨毛膜速性腺激素
hyperemesis gravidarum - 妊娠劇吐
morning sickness - 害喜
nipples - 乳頭
oedema - 水腫
oocyte - 卵子
ovaries - 卵巢
ovulation - 排卵
oxytocin - 催產素
perineum - 會陰
placenta - 胎盤
pruritus - 痕癢
striae gravidarum - 妊娠紋
uterus - 子宮
vagina - 陰道

Chapter 3

Physiology of Menstrual Cycle

William S.B. Yeung

Female Reproductive Cycles

Female reproduction occurs in a cyclical manner. In each cycle, cyclical changes occur in the ovary and the endometrium. Successful implantation of an embryo onto the uterine endometrium happens only within a short period of the endometrial cycle (window of implantation). The sex steroids derived from cyclical follicle development of the ovary regulate the development of the endometrium.

Ovarian Cycle

The ovarian cycle can be divided into follicular, preovulatory and luteal phases. The duration of a normal female reproductive cycle is 28 days, but can vary from 25 to 35 days. Variation in cycle length is usually due to variation in duration of the follicular phase; the duration of the luteal phase is relative stable at around 14 days. Cycle length commonly varies at menarche and before menopause. The basic function units in the ovary are the ovarian follicles. They are classified into:

1. Primordial follicles
   - During the embryonic stage, the female primordial germ cells undergo mitosis during their migration into the genital ridges. These cells cease proliferation and become oogonia in the fetal ovary, where they enter meiosis. The meiotic division is interrupted at prophase I. The resulting primary oocytes are surrounded by a single layer of flattened follicular cells to form the primordial follicles.

2. Primary (preantral) follicles
   - The primordial follicles are regularly recruited to develop into primary follicles with formation of zona pellucida surrounding the oocyte and differentiation of follicular cells into granulosa cells and thecal cells expressing gonadotrophin receptors. The mechanism of recruitment is not entirely known, though it is independent of gonadotrophin. It is estimated that these follicles last for 77-85 days.

3. Secondary (antral) follicles
   - Further development leads to the formation of an antrum in the follicles (antral follicles). These follicles last for 8-12 days, which marks the duration of the follicular phase of the ovarian cycle. The follicles respond to gonadotrophin stimulation resulting in proliferation of follicular cells and production of estradiol. As the antrum in the antral follicles contains fluid, they can be identified with transvaginal ultrasound examination. Under ultrasound, the diameter of the follicles increases at about 2 mm per day. In the absence of follicle stimulating hormone (FSH), the antral follicles degenerate and become atretic.
   - Two cells-two gonadotrophins theory
     - The thecal cells express luteinizing hormone (LH) receptor while the granulosa cells express FSH receptor. LH stimulates the thecal cells to synthesize androgen, which diffuses to the nearby granulosa cells. The granulosa cells aromatize the androgen into estrogen upon FSH stimulation.
   - Positive feedback action on estrogen production
     - Estrogen from the granulosa cells stimulates proliferation and inhibits apoptosis of the granulosa cells. This results in the formation of more granulosa cells, producing increasing amount of estrogen, and eventually leading to a surge of estrogen in the late follicular phase.
   - Expression of LH receptor in granulosa cells
     - FSH and estradiol stimulate the formation of LH receptor on the outer layer of the granulosa cells. The receptor is crucial for the follicle to respond to the midcycle LH surge and its development into preovulatory follicle.

4. Tertiary follicles (preovulatory follicles) (30-36 hours)
   - In the tertiary follicles, the oocyte is surrounded by the cumulus oophorus cells and is connected to the follicular wall by a thin stalk of cells. In response to LH surge, the following events happen:
   - The primary oocyte resumes the 1st meiotic division to form the secondary oocyte, which is arrested at metaphase II.

- The outer granulosa cells undergo luteinization (see below) and produce progesterone.
- Rapid expansion of follicular fluid leading to follicle rupture at 30-36 hours post-LH surge. The rupture is facilitated by the stimulatory action of LH on activities of prostaglandins, collagenase and gelatinase in the follicles. The metaphase II oocyte and its surrounding cumulus cells are ovulated.

5. Corpus luteum
   - Upon LH stimulation, the collapsed ovulated follicle is transformed into a corpus luteum containing a yellowish lutein pigment. The corpus luteum lasts about 14 days (luteal phase). Both the granulosa and the thecal cells contribute to its formation. The corpus luteal cells produce progesterone and estrogen. If the woman is not pregnant, luteolysis occurs at the end of the luteal phase due to loss of luteotrophic support from pituitary LH leading to a fall in the levels of progesterone and estradiol in the blood. If the woman conceives during the cycle, the embryo will develop into a blastocyst which implants into the endometrium. The blastocyst secretes human chorionic gonadotrophin which maintains the function of the corpus luteum and there will not be a drop in the blood levels of estradiol and progesterone.

Hormonal Regulation of the Follicular Growth

Interactions of ovarian steroids, pituitary gonadotrophins and hypothalamic gonadotrophin releasing hormone (GnRH) regulate follicular growth. The pituitary portal venous system brings the pulsatile GnRH from the hypothalamus to the pituitary. GnRH stimulates the synthesis and release of FSH and LH from the pituitary. The interactions of the gonadotrophins with the ovarian sex steroids involve both positive and negative feedback mechanisms.

1. Negative feedback in the follicular and luteal phases
   - The rise of FSH in the late luteal phase of the previous cycle and the early follicular phase stimulates growth of the antral follicles, which produce estrogen. Low level of estrogen acts primarily on the hypothalamus affecting GnRH expression to suppress pituitary gonadotropin secretion. A direct action of estradiol on pituitary secretion of gondotrophin has also been demonstrated.
   - In the luteal phase, progesterone also modulates gonadotropin secretion at the hypothalamic level through suppression of GnRH pulse frequency. This action requires an estrogen priming, probably through induction of expression of progesterone receptors in the hypothalamus. Luteolysis in the late luteal phase results in decrease in production of estradiol and progesterone, which in turn causes an upregulation of FSH production for initiation of follicular growth in the following cycle.

2. Positive feedback in the preovulatory phase
   - In response to a high level of estradiol for 2-3 days in the late follicular phase, a positive feedback occurs resulting in midcycle LH surge. The surge is augmented by a small increase in progesterone in the preovulatory phase. GnRH is absolutely required for the LH surge, though an increase in GnRH secretion is not necessary. Instead, there is an increase in the number of gonadotropin-expressing gonadotropes and an increased expression of GnRH receptor in the gonadotropes, indicating that the positive feedback acts through the pituitary.

Endometrial Cycle

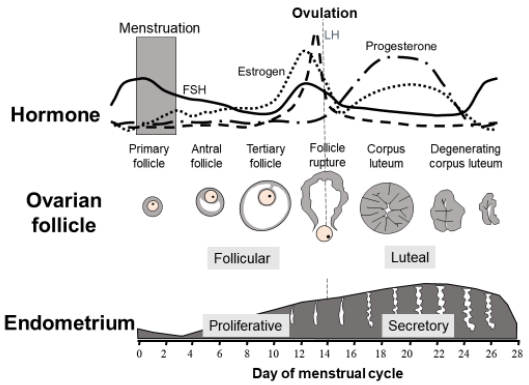
1. The endometrial cycle is divided into proliferative, secretory and menstrual phases. In the proliferative phase, endometrial cells proliferate and the endometrium grow in thickness in response to estradiol from ovarian follicles. In the secretory phase, progesterone from corpus luteum inhibits estradiol-induced proliferation of endometrial cells, and induces secretory transformation of the endometrium; the endometrial glands become tortuous and secretory, and stromal vascularity is increased. The endometrium is receptive to the implanting embryo between 6-10 days post-LH surge (window of implantation), when the level of progesterone is highest.

2. Luteolysis cause a sharp decline in progesterone levels, which triggers menstruation in women. Progesterone withdrawal causes inflammatory response including infiltration of leukocytes, oedema and activation of matrix metalloproteinases, culminating to tissue breakdown and shedding of upper layer of the endometrium in the menstrual phase.

Summary

Changes occur in a female reproductive cycle are summarized in Figure 3.1.

Figure 3.1. Female reproductive cycle.



Clinical Relevance

1. As the length of the luteal phase is constant at around 14 days while the length of the follicular phase is more variable, ovulation usually occurs 14 days before the expected day of the next menstruation i.e Day (usual cycle length - 14). This information can be used to advise woman on the time of her fertile period for fertility treatment or contraception.

2. The development of the ovarian follicles can be monitored by ultrasonography.

3. Ovulation usually occurs about 34-38 hours after the onset of the LH surge. This helps to estimate the time of ovulation for various types of fertility treatment.

4. The serum progesterone level usually peaks at the mid-luteal phase. As the luteal phase lasts for 14 days, the best time to take a blood sample for progesterone assay to assess whether ovulation has occurred in a menstrual cycle is Day (usual cycle length – 7).

Suggested Readings

Strauss J.F. Yen & Jaffe's Reproductive Endocrinology, 7th Edition, 2014. Saunders, Philadelphia.

Johnson M.H. Essential Reproduction. 7th edition, 2013. Wiley-Blackwell, Oxford, UK.

Terms with Chinese Translation

estradiol - 雌二醇
follicle stimulating hormone - 促卵泡激素
follicular phase - 濾泡期／卵泡期
gonadotrophin - 促性腺激素
gonadotrophin releasing hormone - 促性腺激素釋放激素
hypothalamus - 下丘腦
luteal phase - 黃體期
luteinizing hormone - 促黃體激素／黃體生成素
menstruation - 經期
negative feedback - 負反饋
ovulation - 排卵
pituitary - 垂體
positive feedback - 正反饋
progesterone - 黃體激素／孕酮
proliferative phase - 增生期
secretory phase - 分泌期

Chapter 4

Pre-pregnancy and Antenatal Care

Viola Y.T. Chan, Wing-cheong Leung

Pre-pregnancy Care

1. Aims
   - Identify any medical, pharmacological and social risks.
   - Discuss the potential maternal, fetal and neonatal complications arising from pregnancy in relation to the individual's circumstances.
   - Optimize the individual's risk profile to improve pregnancy outcome.
   - Provide general advice on a healthy lifestyle and diet.
   - Provide effective contraceptive advice for women who are not prepared to get pregnant yet.

2. History
   - Age: advanced maternal age (≧35 years old at the time of delivery) is associated with increased risk of infertility, fetal aneuploidy, gestational diabetes, pre-eclampsia and stillbirth
   - Past health: some chronic illnesses affect pregnancy outcome and the disease may be affected by the pregnancy, e.g. poorly controlled diabetes increases risk of congenital malformation, hypertension increases the risk of pre-eclampsia
   - Drug history (teratogens: tetracycline, anti-epileptics, mycophenolate mofetil (MMF), warfarin)
   - Obstetric history
   - Family history: any genetic diseases
   - Social history
   - Substance use - current / past
   - Smoking
   - Alcoholism
   - Domestic violence
   - Social support, financial difficulties.

3. Physical examination
   - Height, weight → BMI
   - Blood pressure, pulse
   - Urine albumin
   - General - pallor, cyanosis, jaundice
   - CVS - heart murmur
   - Chest - wheeze
   - Abdomen - fibroid / mass, scars
   - Pelvic examination.

4. Investigations
   - Cervical smear if not in regular screening programme
   - HBsAg, HIV, Rubella IgG
   - Complete blood count (screening for thalassaemia trait).

5. General advice
   - Healthy lifestyle
   - Optimize BMI (18-25)
   - Folic acid supplementation (400 microgram/day) when planning to get pregnant till 12 weeks pregnancy
   - Vaccination e.g. rubella.

6. Women with underlying medical conditions
   - Multidisciplinary care
   - Optimize underlying medical condition
   - Review +/- adjust medication, stop potential teratogenic drugs if possible
   - Support group.

7. Genetic counselling
   - Women with previous baby / family history of inheritable diseases
   - Three generation pedigree is helpful in assessment
   - Couple with thalassaemia trait
   - If genetic disease identified and at risk of having an affected baby, preimplantation genetic diagnosis or prenatal diagnosis can be discussed.

Antenatal Care

1. Aim
   - Identify risk factors for obstetric complications e.g. venous thromboembolism, fetal growth restriction, gestational diabetes etc., and provide effective preventive measures to reduce the risks
   - Identify maternal, fetal and obstetric complications early and provide timely intervention to reduce maternal and perinatal morbidity and mortality
   - To provide professional advice to mothers and reduce their anxiety including advice on labour and delivery

- To improve family bonding especially if partner / family members are also involved in the antenatal care visits.

2. Schedule of antenatal visits
   - Traditionally
     - Every 4 weeks (booking - 28 weeks)
     - Every 2-3 weeks (28 - 36 weeks)
     - Every week (from 36 weeks)
   - Reduced frequency of antenatal visits was shown to be more cost-effective without increasing preterm birth and low birth weight, but is associated with reduced maternal satisfaction and increased maternal anxiety.
   - Routine antenatal visit
     - History
       - First visit: history as in pre-pregnancy care, last menstrual period (LMP), menstrual cycle, contraception used before pregnancy
       - Maternal complaints
       - Fetal movement if >20 weeks
     - Physical examination
       - Blood pressure (normal: <140/90 mmHg)
       - Body weight (weight gain)
       - Urine for albumin (look for proteinuria)
       - Abdominal palpation - uterine size (symphyseal fundal height (SFH) if >24 weeks), fetal lie, presentation after 30 weeks
       - Fetal heart rate (Doptone)
     - Time for enquiry about any problems and provide advice and reassurance
   - See Table 4.1 for a suggested schedule of antenatal care.

3. Risk assessment
   - Venous thromboembolism (VTE)
     - Personal / family history of VTE, coagulopathy
     - Other risk factors e.g. obesity, advanced maternal age, multiple pregnancy
     - Risk stratification (low/medium/high)
     - Low molecular weight heparin (LMWH) thromboprophylaxis according to risk profile
   - Pre-eclampsia: give low dose aspirin 75 mg to 150 mg from <16 weeks until 36 weeks if any of the following
     - Previous eclampsia / pre-eclampsia
     - Pre-existing hypertension / renal disease
     - Other risk factors e.g. autoimmune disease, advanced maternal age etc
     - 1st trimester pre-eclampsia screening (maternal characteristics, maternal mean arterial BP + uterine artery pulsatility index + maternal serum PIGF, PAPP-A) showing high risk
   - Preterm birth
     - History of preterm births / cervical incompetence
     - Ultrasound surveillance of cervical length +/- cervical cerclage or progesterone if shortened
     - Consider prophylactic cervical cerclage depending on past obstetric history
   - Fetal growth restriction (FGR) / small for gestational age (SGA) fetus
     - Previous history of FGR/SGA fetus
     - Maternal conditions with increased risk of FGR/SGA fetus e.g. pre-eclampsia
     - Serial growth scan + Doppler studies
     - Close monitoring for fetal wellbeing +/- early delivery if fetal wellbeing deteriorates
   - Gestational diabetes
     - Previous history of gestational diabetes
     - Obesity, advanced maternal age, polycystic ovary syndrome
     - Family history of diabetes mellitus
     - Oral glucose tolerance test (OGTT) / dietary advice
   - Screening for fetal aneuploidies
     - NIPT (non-invasive prenatal testing)
     - An important breakthrough in prenatal screening using maternal plasma cell-free fetal (placental) DNA as a non-invasive prenatal testing (NIPT) for fetal chromosomal abnormalities was discovered by Professor Dennis Lo from Hong Kong in 1997
     - NIPT can be performed using maternal blood sample from 10 weeks' gestation onwards
     - NIPT is currently available as a secondary screening tool for pregnancies with positive conventional Down screening as well as for primary screening for Down syndrome
     - The new algorithms in prenatal diagnosis (2022) can be referred to Figure 4.1.

4. Routine antenatal blood tests: clinical implications
   - CBP: low MCV (<80 or 81fl depending on laboratory refererence)
     - test for thalassaemia by Hb electrophoresis
       - Elevated HbA2: beta thalassaemia trait
       - HbH inclusion: alpha thalassaemia trait

  - exclude Fe deficiency anaemia
    - normal Fe but low MCV, assume alpha thalassaemia and test for SEA deletion of alpha globin gene.
  - Check father of fetus for thalassaemia to see if fetus at risk of thalassaemia major, if at risk, refer for prenatal diagnosis. Thalassaemia trait, give folic acid. Fe deficiency, give Fe supplement
- Rh: If Rh negative with a Rh positive fetus, the mother can be sensitized to produce Anti-D antibodies which crosses the placenta causing fetal haemolysis.
  - Rh status of the fetus can be determined non-invasively making use of fetal DNA in maternal circulation.
  - If sensitized prior to this pregnancy (i.e. Rh negative with anti-D antibodies detected), refer to fetal medicine specialist to monitor for fetal anaemia.
  - If Rh positive and anti-D negative, need to prevent sensitization by giving anti-D immunoglobulin.
    - It should be given routinely at 28 weeks (full dose) or 28 weeks and 34 weeks (half dose each), and after delivery.
    - A dose should also be given for events such as heavy vaginal bleeding in first trimester, antepartum haemorrhage, trauma to abdomen, and procedures such as amniocentesis, external cephalic version.
- Syphilis and HIV
  - positive screening needs to be confirmed by further tests to exclude false positive.
  - Prevention of vertical transmission to fetus and neonate is important.
  - Syphilis is usually treated with penicillin.
  - HIV is suppressed by antiretroviral treatment during antenatal period, intrapartum period and early neonatal period
- HBsAg positive
  - prevention of perinatal transmission is important to prevent chronic hepatitis B carrier.
  - Tenofovir (antivirals) is safe in pregnancy (FDA Cat B) and could be given to women with high viral load from 28 weeks to prevent maternal-to-child transmission of HBV.
  - Immunoglobulin should be given together with HBV vaccine to the baby after delivery.

5. Prevention of early onset neonatal group B streptococcus (GBS) infection
   - GBS is an important cause of severe early onset neonatal infection with mortality and morbidity including meningitis.
   - Timely intrapartum antibiotic prophylaxis given to high risk women can effective reduce the GBS colonization rate of newborns and hence the incidence of early onset GBS disease.
   - Universal culture-based screening in Hong Kong has been offered in public obstetric service units since January 2012. The GBS colonisation rate is 21.8% in Hong Kong.
   - For women with previous babies with GBS infection, or with GBS bacteruria any time during pregnancy, intrapartum antibitotics should be given. Screening is not needed.
   - For other women, low vaginal swab and rectal swab are obtained at 35 to 37 weeks gestation to screen for GBS.
   - For women who go into labour before GBS screening is done or before results are available, antibiotic prophylaxis is given during labour based on risk factors, including ruptured membranes>18hours, preterm labour, maternal fever >38^{o}C.
   - Penicillin is most effective for prophylaxis but if history of allergy to penicillin, can use clindamycin or erythromycin as alternatives, but drug resistance need to be checked. Vancomycin can be used in women allergic to penicillin and GBS resistant to clindamycin and erythromycin.

6. Vaccination
   - Diphtheria (reduced dose), tetanus and acellular pertussis (reduced dose) (dTap) vaccine is recommended for women at 26 to 34 weeks of gestation. The antibodies produced can be passed to the fetus before birth for direct protection against pertussis in the first few months of life when the infant has not yet completed his/her own vaccination.
   - Vaccination against influenza and COVID-19 are recommended for pregnant women to reduce risks of severe disease and complications. Antibodies passed to the fetus through the placenta and breast milk could also protect the baby against infection after birth.

7. Planning for labour and delivery:
   - Assessment for plan of delivery is usually done at around 37 weeks gestation, taking into consideration any complications during pregnancy, previous obstetrics history and the lie and presentation of the fetus at 37 weeks.
   - Spontaneous onset of labour and vaginal delivery are the usual plan but there are:
     - Conditions under which labour need to be induced before spontaneous onset because the risk to the fetus or the mother is higher if pregnancy continues futher e.g.
       - Pregnancies going past 41 weeks: risk of fetal death, fetal distress and meconium aspiration increases. Emergency lower segment caesarian section (LSCS) also increases
       - Preeclampsia
       - Fetal growth restriction
       - Prelabour rupture of membranes
     - Conditions under which vaginal delivery is associated with higher risk to the fetus or to the mother e.g.
       - Placenta praevia
       - Breech presentation (early neonatal complications higher in vaginal delivery, can offer external cephalic version at 37 weeks to allow safer vaginal delivery)
       - Previous LSCS: vaginal birth after previous LSCS (VBAC) is usually safe but there is a slight increased risk of uterine rupture and perinatal death compared with repeat elective LSCS, while repeat LSCS carries higher risk for future pregnancies. Mode of delivery needs to be discussed individually at about 37 weeks of gestation
     - If spontaneous labour and vaginal delivery is the initial plan but the women do not go into labour by 41 weeks, assessment should be done again. Sweeping of the membranes can be considered to decrease the need for induction of labour.

8. Malpresentation
   - Definition: presentations other than vertex
   - Types: breech, face, brow, shoulder, compound
   - Causes
     - Prematurity – The fetal position is not stable before term.
     - Conditions with limited space for fetus to turn to vertex presentation such as multiple pregnancy, oligohydramnios, uterine abnormality
     - Conditions associated with persistent unstable position such as hydramnios, multiparity with lax abdominal wall
     - Conditions preventing the engagement of fetal head such as placenta praevia, pelvic tumour and contracted pelvis.
     - Fetal abnormality
   - Breech presentation
     - the fetal lie is longitudinal with the buttocks in the lower pole of the uterus or pelvis.
     - Incidence of breech presentation at term is about 3%.
     - The diagnosis of breech presentation should be suspected on abdominal examination in the antenatal clinic when the fetal head (a hard round and ballotable mass) can be felt in the fundal region instead of the lower pole of the uterus. The buttocks are palpable at or above the pelvic brim.
     - The diagnosis can be confirmed by an ultrasound examination which can also exclude fetal abnormality as well as other conditions predisposing to the occurrence of breech presentation. - Vaginal delivery of a fetus with breech presentation is associated with a higher risk of neonatal complications. Therefore, patients with persistent breech presentation should be counselled for elective LSCS or External Cephalic Version (ECV) to turn the breech presentation into a cephalic presentation.
     - Complications of ECV include: fetal distress or even fetal death, preterm labour, abruptio placentae, and vaginal bleeding.
   - Shoulder presentation
     - Fetal lie is transverse or oblique with the fetal head in the flank of the abdomen or iliac fossa
     - Incidence: one in every 200 deliveries
     - Diagnosis can be confirmed by abdominal ultrasound examination which can also exclude fetal abnormalities, placenta praevia etc.
     - If the transverse/oblique lie persists till 37 weeks, the patient is admitted into the hospital because of risk of prolapse of umbilical cord when the membranes rupture.
     - If the transverse/oblique lie persists till 39 weeks, ECV can be performed if there is no contraindication. If the ECV is successful, the patient may undergo induction of labour by rupturing the membranes and oxytocin infusion (stabilizing induction). If ECV fails, and

the transverse/oblique lie persists, vaginal delivery is not possible. LSCS is indicated.

- Face, brow and compound presentations
  - These are rare and usually diagnosed on vaginal examination when the patient is in labour.

Key Points

- Ideally, all women should have pre-pregnancy care before planning pregnancy to optimize their health and to prepare for pregnancy.
- Pre-pregnancy folic supplement decreases the risk of fetal neural tube defects.
- The aim of antenatal care is to detect maternal, fetal and obstetrical complications early and to treat these early.
- Antenatal care should start between 8-13 weeks gestation.
- A schedule for antenatal care with specified purposes for each visit according to the gestational age is provided in this chapter and can be followed for low risk pregnancies.
- The clinical application of NIPT in prenatal diagnosis is discussed.

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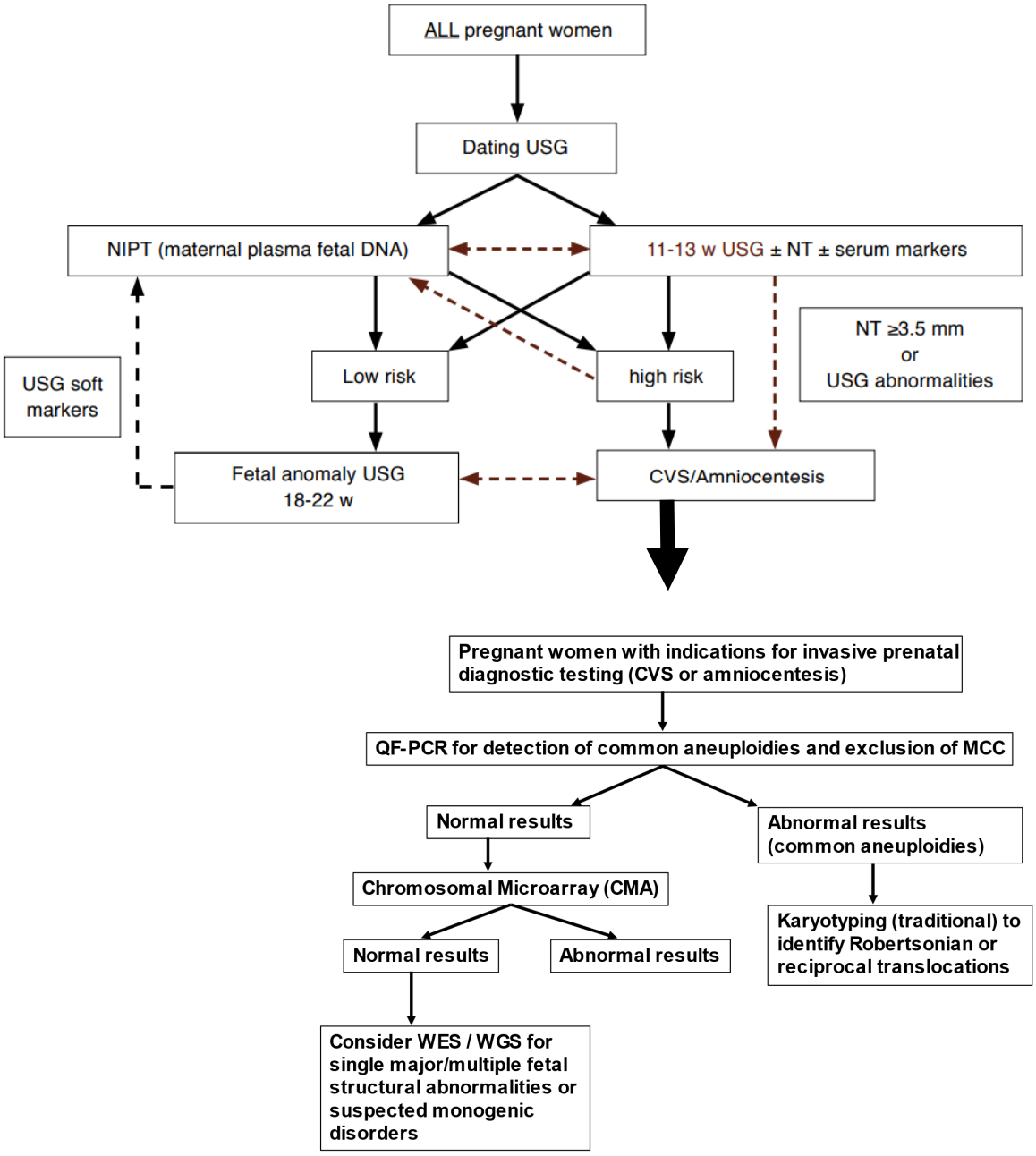
Terms with Chinese Translation

advanced maternal age - 高齡妊娠
analgesia - 止痛／鎮痛
antenatal care - 產前檢查
breech presentation - 臀先露
brow presentation - 眉頭先露
cervical cerclage - 宮頸環扎
cervical incompetence - 宮頸機能不全
cervical smear - 子宮頸抹片／子宮頸塗片
compound presentation - 複合先露
congenital malformation - 先天缺陷
contraception - 避孕
delivery - 生產
Down screening - 唐氏綜合症篩查
face presentation - 面先露
fetal growth restriction (FGR) - 胎兒生長受限
fetal movement - 胎動
folic acid - 葉酸
gestational diabetes - 妊娠糖尿
group B streptococcus - B 型鏈球菌
HIV - 愛滋病毒
induction of labour - 催產／催生
infertility - 不孕／不育
multiparous - 歷產
NIPT - 無創產前 DNA 檢測
oral glucose tolerance test (OGTT) - 口服葡萄糖耐性測試
pre-eclampsia - 先兆子癇
preimplantation genetic diagnosis - 植入前遺傳診斷
prenatal diagnosis - 產前診斷
preterm birth - 早產
primiparous - 初產
rubella - 風疹／德國麻疹
shoulder presentation - 肩先露
small for gestational age (SGA) - 小於孕齡
stillbirth - 死產
syphilis - 梅毒
teratogenic - 致畸性
thalassaemia - 地中海貧血
thromboembolism - 血栓
ultrasound - 超音波／超聲波

Table 4.1 A suggested schedule of antenatal care

Gestation		
8-13 weeks	Booking Visit	Ultrasound for dating (Nuchal translucency if 11-13 weeks, +hCG/AFP for Down screening) Folic acid (400mcg/ day, 5mg /day if high risk of fetal neural tube defect) Risk assessment (VTE/Preterm birth/PET/FGR) * Full physical examination (PV only if indicated) Lifestyle advice Routine antenatal blood tests (Complete blood count, Rh Blood Group, Rubella antibody, Hepatitis surface antigen, Anti-HIV, Syphilis) OGTT if high risk for DM, otherwise, fasting glucose
13-18 weeks	Down screening	If book after 13 weeks, maternal serum markers for Down screening in 2nd trimester
18-22 weeks	Routine scan	Detection rate of major congenital malformation 70% If placenta reached cervical os, repeat ultrasound at 30 weeks for placental location
28 weeks	Blood tests	CBC- identify and treat anaemia OGTT
35-37 weeks	GBS screening Plan of delivery	Low vaginal and rectal swab for group B streptococcus screening Discuss mode of delivery, analgesia, birth plan
>40 weeks	Discuss induction of labour after 41 weeks	Optional: membrane sweeping at 40 weeks for primiparous woman, and 41 weeks for multiparous women with an aim to reduce induction of labour

Figure 4.1 New Algorithms in Prenatal Screening & Diagnosis in HKSAR (2022)



CMA = chromosomal microarray (molecular karyotyping), detecting microdeletions & microduplications; CVS = chorionic villus sampling; MCC = maternal cell contamination; NIPT = noninvasive prenatal testing; NT = nuchal translucency; QF-PCR (RAT) = quantitative fluorescent polymerase chain reaction (rapid aneuploidy testing); USG = ultrasound; WES = whole exome sequencing; WGS = whole genome sequencing

Chapter 5

Hypertension in Pregnancy

Ah-lai Liu, Wing-cheong Leung

Introduction

Hypertensive disorder in pregnancy is a common complication during pregnancy. It occurs in 2 to 8% of pregnancies. The number of maternal deaths due to hypertensive disorders in pregnancy had fallen steadily in recent few decades. However, it remains a major cause of maternal and perinatal morbidity and mortality.

Definitions and Diagnosis

1. Hypertension – defined as blood pressure (BP) ≥140/90 mmHg with at least two readings taken four hours apart.
   - Severe hypertension: BP ≥ 160/110 mmHg.

2. Significant proteinuria – defined as urinary protein:creatinine ratio ≥30 mg/mmol, or albumin:creatinine ratio ≥8 mg/mmol or >300 mg/day of protein in 24-hour urine.

3. Placental growth factor (PIGF)-based testing can help to rule out but not rule in (diagnose) pre-eclampsia between 20 weeks and 35 weeks.

4. Chronic hypertension - hypertension diagnosed before 20 weeks gestation of pregnancy.
   - Chronic hypertension - hypertension diagnosed before 20 weeks gestation of pregnancy without significant proteinuria.
   - Chronic renal disease - significant proteinuria presenting before 20 weeks with or without hypertension.
   - Chronic hypertension with superimposed pre-eclampsia - hypertension diagnosed before 20 weeks gestation of pregnancy without significant proteinuria with proteinuria detected after 20 weeks.

5. New onset hypertension with or without proteinuria in pregnancy.
   - Gestational hypertension - new onset hypertension presenting after 20 weeks without significant proteinuria.
   - Gestational proteinuria – new onset significant proteinuria presenting after 20 weeks without hypertension.
   - Pre-eclampsia - new onset hypertension presenting after 20 weeks with significant proteinuria.

6. Eclampsia – a convulsive condition associated with pre-eclampsia.

7. HELLP syndrome – haemolysis, elevated liver enzymes and low platelet count.

Table 5.1. Definitions for hypertensive disorders in pregnancy.

20 weeks

Chronic hypertension	New onset hypertension +/- proteinuria in pregnancy
Chronic hypertension (no proteinuria)	Gestational hypertension (no proteinuria)
Chronic renal disease (proteinuria +/- hypertension)	Gestational proteinuria (no hypertension)
Chronic hypertension with superimposed pre-eclampsia (new onset proteinuria after 20 weeks)	Pre-eclampsia (hypertension with proteinuria)

Prevention

1. Blood pressure should be measured at every antenatal visit.

2. All pregnant women should be advised to seek immediate medical advice if symptoms of severe pre-eclampsia including
   - Severe headache
   - Problems with vision e.g. blurring / flashing
   - Epigastric pain
   - Vomiting
   - Sudden swelling of face, hands or feet.

3. Use of low dose aspirin
   - A Cochrane review showed reduction in risk of developing pre-eclampsia, with greater risk reduction in high-risk groups.
   - Advise use of low dose aspirin 75 mg to 150 mg daily orally from 12 weeks to 36 weeks in patients with risk factors for pre-eclampsia. Table 5.2 shows the risk factors for considering low dose aspirin. Aspirin should preferably be started ≤ 16weeks, but starting after 16weeks might still be beneficial.

4. First trimester pre-eclampsia screening, involved combined
   - Maternal history / characteristics
   - Uterine artery Doppler study
   - Biochemical markers
     - maternal serum placental growth factor (PIGF)
     - pregnancy-associated plasma protein A (PAPP-A)
   - Results showed good detection rate of early onset pre-eclampsia but not perform well on predicting late onset pre-eclampsia (which is more common), also FPR 5-10% potentially increase intervention and anxiety.

Complications

1. Pre-eclampsia can lead to a number of serious complications if left untreated. Therefore pre-eclampsia should be diagnosed and managed timely and actively.

2. Complications of pre-eclampsia include:
   - Placental abruption (in which may lead to disseminated intravascular coagulopathy, intrauterine death)
   - Cerebral haemorrhage
   - Eclampsia
   - Pulmonary oedema
   - Fetal growth restriction (FGR).

Table 5.2. Risk factors for considering low dose aspirin.

High risk (Any one)	**Moderate risk** (Two or above)
Hypertensive disease during a previous pregnancy	First pregnancy
Chronic kidney disease	≥40 years old
Autoimmune disease e.g. SLE, APL syndrome	Pregnancy interval >10 years
Type 1 or Type 2 DM	BMI ≥35 kg/m^2 at first visit
Chronic hypertension	Family history of PET
	Multiple pregnancy

Management

1. Management of chronic hypertension and gestational hypertension
   - Treatment of hypertension
     - Angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and chlorothiazides should be stopped and switch to alternative medications
     - Choice of antihypertensives includes: labetalol, methyldopa and nifedipine
     - Target BP 135 / 85mmHg
     - Multidisciplinary management if chronic renal disease.
   - Prevention of pre-eclampsia: low dose aspirin between 12 weeks and 36 weeks if chronic hypertension.
   - Monitor maternal well-being
     - Regular follow up with monitoring of BP and evidence of proteinuria, frequency depending on severity of hypertension
     - Measure CBC, LRFT at diagnosis of gestational hypertension then weekly
     - Carry out PIGF-based testing on one occasional if suspicious of pre-eclampsia.
   - Monitor fetal well-being
     - Ultrasound examination for fetal growth, liquor volume and Doppler studies at 28, 32, 36weeks for chronic hypertension, and at diagnosis of gestational hypertension then 2-4weekly if clinically indicated
     - Perform cardiotocography (CTG) only if indicated.
   - Timing of delivery
     - Do not offer planned early birth <37weeks if BP <160/110mmHg
     - If planned early birth is indicated, offer a course of antenatal corticosteroids and magnesium sulfate for neuroprotection if indicated.

2. Management of pre-eclampsia
   - Admit patient for in-patient assessment if clinical concerns, full PIERS (Pre-eclampsia Integrated Estimate of RiSk) or PREP-S (Prediction model for Risks of complications in Early-onset Pre-eclampsia) high risk or severe hypertension.
   - Treatment of hypertension
     - Start antihypertensive if BP >140/90 mmHg
     - First-line antihypertensive is labetalol, nifedipine if labetalol not suitable, methyldopa if both labetalol and nifedipine not suitable
     - Target BP 135/85 mmHg.
   - Monitor maternal well-being
     - Measure BP regularly, every 15-30min if severe hypertension, at least 4 times a day if inpatient
     - Monitor for symptoms of severe pre-eclampsia.
   - Check complete blood count (CBC), liver and renal function tests (LRFT) 2-3 times a week.
   - Monitor fetal well-being
     - Ultrasound examination for fetal growth, liquor volume and Doppler studies at diagnosis then every 2 weeks
     - CTG at diagnosis, and then if clinically indicated.
   - Timing of delivery
     - Threshold for delivery before 37 weeks
       - Unable to control BP despite 3 or more classes of antihypertensives in appropriate doses
       - SaO2 <90%
       - Deterioration in maternal haemotological / biochemical markers (LFT, RFT, platelet count, haemolysis)
       - Ongoing neurological features
       - Placental abruption
       - Fetal indication: reversed end diastolic flow on fetal umbilical artery doppler, abnormal CTG, stillbirth
       - If planned early birth is indicated, offer a course of antenatal corticosteroids and magnesium sulfate for neuroprotection if indicated
     - After 37 weeks
       - Recommend delivery within 24-48 hours if diagnosis of pre-eclampsia established.

3. Intrapartum management
   - Monitoring
     - BP and pulse at least every hour, every 15-30min if severe hypertension
     - Foley catheter, monitor urine output every hour (should be >20 ml/hour)
     - Oxygen saturation (SaO2) monitoring, if <95% consider medical review for possible pulmonary edema
     - Strict fluid balance, monitor input / output, fluid restriction to 80 ml/hour
     - Respiratory rate every one hour, if using magnesium sulphate (MgSO4)
     - Temperature every 4 hours
     - Central venous pressure (CVP), if urine output unsatisfactory
     - Neurological assessment (e.g. Glasgow coma scale score) every one hour

- Continuous fetal heart monitoring
- Blood tests (CBC, LRFT, urate, clotting profile) every 12 hours or when clinically indicated.

- Medical treatment
  - MgSO4
    - Consider if one or more features of severe pre-eclampsia, if birth is planned within 24hrs or if eclamptic fit
    - Dosage: 4 g loading dose intravenously (IV) over 5-15 minutes, then infusion 1 g/hour IV maintained for 24 hours after delivery or last fit
    - If recurrent seizure while on MgSO4: further dose 2-4g loading over 5-15 minutes
    - While on MgSO4, monitor respiratory rate, patellar reflex, urine output hourly to prevent magnesium toxicity, check serum Mg level if urine output <30 ml/hour
    - If seizure recurred after 2 loading doses, consider IV diazepam 10 mg
    - If focal seizure or focal neurological deficit after cessation of seizure, consider cerebral haemorrhage
  - Antihypertensives (target BP <150/80-100 mmHg)
    - Labetalol (oral or IV)
      - Oral: 100 mg every 45min, maximum 1200 mg/day
      - IV: 20 mg loading dose, 20-80 mg every 30 minutes, maximum 300 mg
    - Nifedipine (oral, contraindicated in coronary artery disease, aortic stenosis, diabetes mellitus >15 yrs) 5 mg first dose, then 10 mg every 30 minutes
    - Hydralazine (IV)
      - 5-10 mg every 30 minutes, maximum 20 mg
  - Steroid prophylaxis
    - Betamethasone 12 mg intramuscular every 24 hours for 2 doses if early birth is likely within 7 days and antenatal corticosteroids indicated for gestation
  - Thromboprophylaxis.
- Multidisciplinary management
  - Anaesthetist
    - Eclampsia – secure airway
    - Delivery – pain relief / caesarean delivery
    - Do not preload with IV fluid before epidural anaesthesia
  - Paediatrician
    - Neonatal intensive care unit (NICU) bed availability
    - Consider in-utero transfer if maternal condition stable and NICU bed not available
  - ICU
    - Consult ICU team for support if complications from severe pre-eclampsia
  - Medical / neurosurgical if clinically indicated.
- Delivery
  - Mode of delivery - clinical circumstances
  - Consider operative delivery to shorten second stage if severe hypertension
  - Third stage: avoid ergometrine or ergometrine containing drugs (e.g. syntometrine).

4. Postnatal management
   - Monitor and control BP (aim: <150/100 mmHg).
   - Choice of antihypertensives: Enalapril, nifedipine, amlodipine, atenolol/ labetalol. Use once daily regime if possible.
   - Consider changing methyldopa to other antihypertensives because of risk of postpartum depression.
   - Fluid balance.
   - Continue MgSO4 for 24 hours after delivery.
   - SaO2 monitoring for 24 hours.
   - Watch for symptoms of shortness of breath.
   - Breastfeeding
     - Avoid diuretics / angiotensin receptor blockers
     - Safe for breastfeeding: labetalol, nifedipine, enalapril, captopril, atenolol, metoprolol.
   - Postnatal review
     - Medical review 6-8 weeks after birth, if still needs antihypertensive or proteinuria, refer specialist for continued management
     - Risk of recurrence in future pregnancies
       - Gestational hypertension – ~22%
       - Preeclampsia – ~ 16%
       - If previous severe pre-eclampsia or HELLP or eclampsia or led to birth <34 weeks - ~33%, if 34 - 37weeks ~23%.

Key Points

- Hypertensive disorder in pregnancy is a major cause of maternal and perinatal morbidity and mortality.
- Pre-eclampsia is defined as new onset hypertension presenting after 20 weeks with significant proteinuria.
- Use of low dose aspirin between 12weeks and 36weeks in patients with risk factors of pre-eclampsia.
- Management of hypertensive disorder in pregnancy involves treatment of hypertension, monitor maternal status, monitor fetal status and decide time and mode of delivery.
- MgSO4 is the choice of anti-convulsant at eclampsia.
- Multidisciplinary approach should be adopted if necessary.

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Terms with Chinese Translation

eclampsia - 子癇症
gestational hypertension - 妊娠高血壓
gestational proteinuria - 妊娠蛋白尿
pre-eclampsia - 先兆子癇症

Chapter 6

Gestational Diabetes

Cherrie W.K. Yung, Wai-lam Lau

Definitions and Diagnosis

Hyperglycemia first detected at any time during pregnancy should be classified as either:

1. Diabetes mellitus in pregnancy
   - If one or more of the following criteria are met:
     - Fasting plasma glucose ≥7.0 mmol/l
     - 2-hour plasma glucose ≥11.1 mmol/l following a 75g oral glucose tolerance test (OGTT)
     - Random plasma glucose ≥ 11.1 mmol/l in the presence of diabetes symptoms.

2. Gestational diabetes mellitus (GDM)
   - By the 2013 World Health Organization criteria if one or more of the following criteria are met:
     - Fasting plasma glucose 5.1-6.9 mmol/l
     - 1-hour plasma glucose ≥10.0 mmol/l following a 75g OGTT
     - 2-hour plasma glucose 8.5-11.0 mmol/l following a 75g OGTT.

Prevalence

1. The prevalence of GDM in a population varies directly to the prevalence of type 2 diabetes mellitus (DM). In Hong Kong, the prevalence is about 10-14%.

2. In most cases, diagnosis is made after a screening test in late second or early third trimester.

3. Women developing GDM in pregnancy are at risk of type 2 diabetes in their future life.

Pathophysiology

1. During pregnancy, insulin resistance progressively increases (up to 50% in late pregnancy) due to:
   - increase in maternal adipose tissue
   - hormones produced by the placenta.

2. Insulin does not cross placenta. From 11th or 12th week of gestation, the fetal pancreas is capable of responding to hyperglycemia. The fetus then becomes hyperinsulinemic, which promotes growth and macrosomia.

Complications

1. Untreated or poorly controlled GDM increases the risk of adverse maternal and fetal outcome. With early recognition and optimal control, the risk can be significantly reduced.

2. Maternal complications
   - Pregnancy-induced hypertension and pre-eclampsia.
   - Vulvo-vaginal infection, urinary tract infection.
   - Cephalopelvic disproportion: increased risk of operative delivery
   - Long term development of type 2 DM.

3. Fetal complications
   - Large-for-gestational-age or macrosomia (increased risk of shoulder dystocia, birth trauma)
   - Polyhydramnios
   - Prematurity
   - Respiratory distress syndrome: fetal hyperinsulinaemia suppresses surfactant production
   - Neonatal complications: jaundice, polycythemia, hypocalcemia, hypomagnesemia, hypoglycemia
   - Stillbirth: in cases of suboptimal control
   - Increased risk of obesity and diabetes in childhood and adulthood.

Screening

GDM is associated with adverse pregnancy outcome and is usually asymptomatic. Adverse pregnancy outcome can be decreased by treatment. Therefore screening is necessary. There are two approaches to screening:

1. Universal screening: OGTT at 24-28 weeks for all pregnant women is effective but expensive, should be offered if resources allow

2. Selective screening, if resources are limited. OGTT is performed for high risk group identified based on the following factors:
   - History
     - Previous GDM
     - Previous macrosomic baby
     - Previous recurrent miscarriage

- Previous unexplained stillbirth, neonatal death or congenital malformation
- Previous pre-eclampsia
- Known polycystic ovarian syndrome
- Long term use of corticosteroid
- Family history (first degree relatives) of DM.

- Current pregnancy
  - Advance maternal age (≥35 years old)
  - High body mass index (≥25)
  - Large-for-gestational-age (LGA) fetus
  - Polyhydramnios
  - Multiple pregnancy
  - Glycosuria (based on strip test, 2+ on one occasion or 1+ on two occasions).

Management

Dietary control and insulin - aim to maintain normoglycemia (ideal target: fasting ≤5.3 mmol/l, 2 hours postprandial ≤6.8 mmol/l).

1. Dietary control (for all GDM women)
   - Refer to dietitian.
   - 30-35 kcal/kg pre-pregnant weight per day for non-obese women and 25 kcal/kg for obese women, with additional 300 kcal per day per fetus.
   - Divided into 3 main meals with snacks in between.
   - Snack at bedtime is recommended to prevent hypoglycemia and starvation ketosis.
   - Regular exercise (such as 30 minutes walking after meal) to improve glucose control.

2. Insulin should be started
   - If diet restriction for 2 weeks fails to achieve normoglycemia, insulin therapy should be considered.
   - At diagnosis, together with diet control for women with high fasting glucose (≥7.0 mmol/l, or 6.0-6.9 mmol/l with macrosomia and polyhydramnios).
   - Insulin is safe in pregnancy. Common schedule used:
     - Short acting insulin pre-meal (for 3 main meals)
     - Medium-acting insulin before bed-time, if necessary.

3. Oral hypoglycaemic agent (OHA)
   - Increasing evidence in using OHA to treat GDM
     - Systemic reviews show that it is effective with similar short term outcome comparing to insulin
   - Metformin is preferred.
   - Although OHA crosses placenta, it is regarded as a reasonable alternative for treating GDM, to be used alone or in addition to insulin treatment especially in 2nd or 3rd trimester of pregnancy

4. Monitoring of glucose control
   - Glycemic control should be monitored regularly by capillary glucose measurement.
   - Frequency can vary from weekly to daily, depending on the maternal and fetal condition.
   - In pregnancy, post-meal glucose is more important as fetus is more sensitive to hyperglycemia.
   - For patients requiring insulin therapy, both fasting, pre-meal and post-meal glucose monitoring is advised.
   - Home monitoring is more effective.
   - Haemoglobin A1c (≤ 6.5%).
   - Avoid hypoglycaemia.

5. Fetal monitoring
   - No universally agreed protocol on fetal monitoring for GDM.
   - Poorly controlled GDM is associated with increased risk of fetal demise.
   - Ultrasound monitoring of fetal growth and amniotic fluid volume.
   - Antepartum cardiotocography (CTG) for fetal well-being.

6. Delivery
   - Time of delivery
     - Well controlled GDM on diet only and without complications: around 40 weeks
     - Well controlled GDM on insulin and without complications: 38-39 weeks
     - Suboptimal controlled GDM, or with fetal complications (e.g. polyhydramnios or macrosomia): individualized, may need to be earlier than 38 weeks.
   - Mode of delivery
     - If macrosomia (≥4 or 4.5 kg), caesarean section to avoid shoulder dystocia.
   - Intrapartum monitoring
     - CTG to monitor fetus
     - Women on diet therapy alone do not require any specific measures during labour
     - Women on insulin therapy require hourly monitoring of glucose level and infusion of insulin with 10% dextrose and potassium chloride based on sliding scale.

7. Puerperium
   - After delivery, the influence of placental hormone dissipate rapidly; most women revert back to their prepregnancy glycemic status almost immediately
     - For women on diet therapy, normal diet can be resumed
     - For women on insulin therapy, check glucose level for 24 to 72 hours after delivery as they may have pre-existing DM.
   - Postpartum fasting glucose or OGTT 6-8 weeks after delivery should be arranged to exclude pre-existing DM.
   - Breastfeeding should be encouraged
     - Improves maternal glucose metabolism
     - Many other potential benefits to mother and baby.
   - Contraception
     - No special contraindication regarding to the GDM status only
     - Note the limitation from other coexisting risk factors e.g. obesity.

8. Long term implications
   - Increased risk in developing type 2 DM.
   - Prevention (exercise and dietary advice) and follow-up (yearly fasting blood glucose or OGTT) is recommended.

Key Points

- Gestational diabetes is a common medical complication associated with increased maternal and fetal risk during pregnancy.
- Screening is important to identify the affected mothers before complications arise.
- Effective control and monitoring improve pregnancy outcome.
- Antenatal, intrapartum and postpartum management should be modified.
- Multidisciplinary care is required for management of gestational diabetes.

Suggested Readings

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Terms with Chinese Translation

gestational diabetes - 妊娠糖尿病
macrosomia - 巨大兒
neonatal death - 新生兒死亡
polyhydramnios - 羊胎水過多
pre-eclampsia - 先兆子癇

Chapter 7

Pregnant Women with Pre-existing and Co-incidental Diseases

Annisa S.L. Mak, Kwok-yin Leung

Introduction

1. Pre-existing disease can affect pregnancy and vice versa.

2. Most women remain well throughout their pregnancy, but some women are at risk of severe morbidity or even mortality.

3. A multi-disciplinary team approach to provide optimal management.

4. Pre-pregnancy counselling should be provided.

5. Medications which are safe in pregnancy can be used as appropriate.

Renal Diseases

1. Urinary tract infection (UTI)
   - Common in pregnancy
   - Risk factors: history of recurrent cystitis, renal tract abnormality, diabetes or bladder emptying problem.
   - Asymptomatic bacteriuria (count exceeds 100,000/mL on a mid-stream urine specimen) occurs in 4-7% of pregnant women.
   - Untreated bacteriuria may be associated with an increased risk of preterm birth, low birth weight, and perinatal mortality.
   - Asymptomatic bacteriuria should be treated to reduce the risk of progression to UTI or even pyelonephritis.
   - Symptoms of UTI can be atypical, and the classic presentation of UTI including frequency, dysuria and haematuria may not be present in pregnancy.
   - Acute pyelonephritis during pregnancy is suggested by the presence of flank pain, nausea/vomiting, fever >38 degree Celsius, and/or costovertebral angle tenderness, with or without the typical symptoms of cystitis, and is confirmed by the finding of bacteriuria in the setting of these symptoms.
   - Antibiotics can be started before culture results are available when UTI is strongly suspected.
   - Common pathogens include Escherichia Coli, streptococci, proteus, pseudomonas and Klebsiella.
   - Options of antibiotics include ampicillin, amoxicillin, cephalosporins.
   - In-patient care should be provided for acute pyelonephritis with monitoring of renal function, ultrasound of the kidneys to exclude hydronephrosis, maternal congenital renal abnormalities and renal calculi.

2. Chronic renal disease (CRD)
   - Effects of pregnancy on CRD: possible declining renal function, worsening proteinuria, flares or relapse of the disease e.g. glomerulonephritis.
   - Effects of CRD on pregnancy: miscarriage, hypertensive disorders of pregnancy (including gestational hypertension, pre-eclampsia, HELLP syndrome), fetal growth restriction, preterm delivery, intrauterine death or neonatal death.
   - Prognosis depends on the degree of renal impairment, severity of hypertension, degree of proteinuria, type and progress of CRD, and whether there is superimposed pre-eclampsia.
   - The prognosis of pregnancy with a stable CRD, and without of renal impairment, hypertension, proteinuria or pre-eclampsia, is favorable.
   - Women with severe renal impairment should be advised to avoid pregnancy.
   - Antenatal management: monitoring of blood pressure, proteinuria, and renal function, control of hypertension, early detection of superimposed pre-eclampsia and fetal monitoring.
   - Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) should be avoided.
   - Vaginal delivery is the preferred mode of delivery if there are no obstetric contraindications.
   - Postpartum care is similar among women with and with chronic renal disease.

Cardiac Diseases

1. Incidence and risks
   - Congenital heart disease (CHD) becomes more common among pregnant women.
   - Pregnancy can affect cardiac function because of physiological increase in blood volume, heart rate and cardiac output.
   - Maternal risks: Heart failure, infective endocarditis, cardiac arrhythmia, and cardiomyopathy.
   - Fetal risks: fetal growth restriction and preterm delivery (especially in cardiac disease with restricted cardiac output e.g. coarctation of aorta or cyanotic heart disease).
   - The risk of fetus inheriting cardiac defects is raised significantly, where the risk is approximately 1%. Heritability varies between 3 and 50% depending on the type of parental heart disease.

2. Modified World Health Organization (WHO) classification
   - Class I: No detectable increased risk of maternal mortality or mild increase in morbidity. Examples are uncomplicated small or mild pulmonary stenosis or repaired ventricular septal defect.
   - Class II: small increased risk of maternal mortality or moderate increase in morbidity. Examples are unoperated septal defect, repaired tetralogy of Fallot, and most arrhythmias.
   - Class II-III: Intermediate increased risk of maternal mortality or moderate to severe increase in morbidity. Examples are mild left ventricular impairment, hypertrophic cardiomyopathy.
   - Class III: Significantly increased risk of maternal mortality or severe morbidity. Examples are mechanical heart valve, unrepaired cyanotic CHD, moderate mitral stenosis. Expert counselling is required concerning pregnancy.
   - Class IV: Extremely high risk of maternal mortality or severe morbidity. Examples are pulmonary arterial hypertension, severe systemic ventricular dysfunction, vascular Ehlers-Danlos etc. Pregnancy is contraindicated.

3. Antepartum management
   - Antepartum management: multidisciplinary care with pregnancy heart team, involving cardiologist, obstetrician and anesthetist.
   - Correction of factors that may lead to decompensation: anemia, infection, hypertension, and arrhythmias.
   - Signs and symptoms of possible decompensation: nocturnal dyspnea, change in heart rate or rhythm, malaise or reduced exercise tolerance.
   - Adequate rest, but hospitalization for bed rest only for women with deteriorating cardiac status.
   - Low molecular weight heparin is the drug of choice for the prevention and treatment of venous thromboembolism in pregnant patients.
   - Fetal echocardiography should be offered, and detailed scanning to identify associated anomalies should be arranged.
   - Serial ultrasound examinations for fetal growth indicated for women with restrictive cardiac output or cyanosis.

4. Intrapartum management
   - Ideally, women with significant cardiac disease should be delivered in a unit with availability of experienced obstetricians, cardiologists, anaesthetists and midwives.
   - Induction of labour at term may be considered in women with cardiac disease without contraindications for vaginal delivery.
   - Caesarean delivery should be considered in patients with previous aortic dissection, aggressive aortic pathology, in acute intractable heart failure and in severe forms of pulmonary hypertension.
   - Aortocaval compression and fluid overload should be avoided.
   - Prophylactic antibiotics for prevention of endocarditis should be considered in some women.
   - Adequate pain relief.
   - Monitoring of cardiac heart rate, oxygen saturation and arterial blood pressure.
   - Second stage should be shortened with the use of instrumental delivery if necessary.
   - Ergometrine should be avoided, use oxytocin only to reduce blood loss.

5. Postpartum management
   - Minimize risk of postpartum hemorrhage
   - The postpartum period is associated with significant haemodynamic changes and fluid shifts, which may precipitate heart failure.
   - Haemodynamic monitoring should be continued for at least 24-48 hours in those at risk.
   - Other potential complications include infective endocarditis and deep vein thrombosis.

Liver Diseases and Gastrointestinal Diseases

1. Non-alcoholic fatty liver disease
   - Non-alcoholic fatty liver disease is usually discovered incidentally by detecting elevated transaminases on routine investigation, and no other underlying cause is found.
   - Definitive diagnosis can be made with a liver biopsy, which is rarely indicated during pregnancy.
   - Undesirable consequences include liver fibrosis or cirrhosis, hepatocellular carcinoma, and progression to type 2 diabetes.
   - Treatment is with weight loss, exercise, healthy diet and avoidance of alcohol.

2. Viral hepatitis
   - Hepatitis A
     - transmitted through oral-fecal route
     - usually a benign illness but occasionally fulminating hepatitis
     - manage as in non-pregnant patients
     - Vertical transmission is rare, but may occur if the mother develops hepatitis A at or around the time of delivery.
   - Hepatitis B
     - Transmitted through sex, blood, and vertical from mother to baby
     - Acute infection: can be severe but most are asymptomatic, manage as in non-pregnant patients
     - Chronic carriers: vertical transmission is prevented by universal prenatal screening of maternal blood for hepatitis B surface antigen (HBsAg) at antenatal booking, and if positive, administration of hepatitis B immune globulin as well as vaccination to baby at birth. To prevent antenatal transmission, the recent recommendation is to give antiviral therapy to women with high viral load in the third trimester.
     - Referral to medical for multidisciplinary care if appropriate
   - Hepatitis C
     - Transmitted through blood, sex and vertical from mother to baby
     - Acute infection often asymptomatic, but more than half have active hepatitis which will progress to cirrhosis or even hepatocellular carcinoma.
     - Vertical transmission is uncommon
   - Other pathogens associated with viral hepatitis include Hepatitis virus D or E, Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Herpes Simplex virus (HSV)

3. Inflammatory bowel disease
   - Crohn's disease (CD) and ulcerative colitis (UC)
   - Pregnancy is associated with an increased risk of flare of UC but not of CD
   - Most changes in disease activity occur in the first two trimesters, and active disease at the time of conception or during pregnancy may adversely affect the pregnancy.
   - Topical and oral 5-aminosalicylates (salfasalazine, mesalazine), oral and rectal corticosteroid and oral thiopurines are safe to use in pregnancy and during breast-feeding.
   - Data are accumulating for the safety of anti-TNF α agents and other biologics in pregnancy.
   - Elective caesarean section is usually not necessary, even in women with ileostomies, except in women with obstetric indications, peri-anal CD or some women with pouches.

4. Peptic ulceration
   - Symptoms: epigastric pain which may be relieved by food in cases of duodenal ulcer or aggravated by food in cases of a gastric ulcer.
   - The increase in prostaglandin production in pregnancy has a protective effect on the gastric mucosa.
   - Oesophagogastroduodenoscopy can be considered in pregnancy.
   - Regular antacids, sucralfate, H2-receptor blockers and proton-pump inhibitors are safe in pregnancy, but misoprostol, a prostaglandin analogue, is contraindicated in pregnancy since it induces uterine contraction.
   - H- pylori eradication therapy can usually be deferred until after pregnancy.

Respiratory Diseases

1. Asthma
   - Asthma may improve, deteriorate or remain unchanged during pregnancy.
   - Effects of asthma on pregnancy are usually small if the condition is well controlled. Pregnancy itself does not usually influence the severity of asthma.
   - Deterioration common in those who have self-stopped their usual medication during pregnancy.
   - Inhaled and intravenous β2 -agonist as well as inhaled, oral and intravenous steroids are safe in pregnancy and while breastfeeding.
   - Intrapartum steroid cover is required for women receiving oral steroids at a higher dose, and until oral medication is restarted.

- Pain relief in labour, including epidural analgesia and Entonox can be used by women with asthma, although opiates for pain relief should only be used with extreme caution in the event of an acute severe asthmatic attack.
- Regional anesthesia is preferable rather than general anaesthesia because of the decreased risk of chest infection and atelectasis of the former.
- Use of prostaglandin E2 for cervical ripening is safe as it causes bronchodilatation.
- Prostaglandin F2α and ergometrine can cause bronchospasm.
- Pregnant women with asthma should be asked for history of aspirin-sensitivity before starting on prophylactic aspirin for prevention of pre-eclampsia

2. Tuberculosis (TB)
   - Symptoms of TB in early stages may mimic minor ailments of pregnancy
   - When a pregnant woman belonging to high risk group has cough, malaise or weight loss, TB should be suspected
   - Extrapulmonary TB is as common as pulmonary TB in pregnancy.
   - Both TB skin testing and blood tests are safe to use during pregnancy.
   - Chest X ray with abdominal shield can be performed in pregnancy but diagnosis of TB disease should be confirmed bacteriologically.
   - The common causative organism is Mycobacterium tuberculosis.
   - There is little evidence to suggest that pregnancy adversely affects disease progression unless drug compliance was poor.
   - Rifampicin, ethambutol and pyrazinamide and isoniazid are safe in pregnancy, but those on isoniazid should also take pyridoxine to reduce the risk of peripheral neuritis.
   - Streptomycin should be avoided because of auditory nerve toxicity.
   - Vitamin K should be given to mothers on rifampicin since it induces cytochrome P450.
   - Liver function should be monitored regularly due to risk of isoniazid or rifampicin-related hepatotoxicity
   - The baby should be given BCG vaccination.
   - The amounts of anti-tuberculous drugs excreted in breast milk are not sufficient to dissuade women from breastfeeding.

Thyroid Diseases

1. Physiological changes (refer to Chapter 2)
   - Thyroid function test should be interpreted using the reference ranges for pregnancy.

2. Hyperthyroidism
   - Most cases with hyperthyroidism in pregnancy are due to Graves' disease, an autoimmune disease.
   - Thyrotoxicosis often improves during pregnancy but may flare postpartum.
   - Mothers having good control usually have good pregnancy outcomes, but untreated mothers have an increased risk of miscarriage, fetal growth restriction, preterm labour, and perinatal mortality.
   - Transient fetal/ neonatal goitre and thyrotoxicosis could be caused by transplacental transfer of thyroid-simulating antibodies.
   - Maternal complications include atrial fibrillation, gastrointestinal upset, abdominal pain and even psychosis.
   - The symptoms of hyperthyroidism including maternal tachycardia, weight loss, heart murmurs and heat intolerance mimic that of pregnancy.
   - Hyperthyroidism is diagnosed by high levels of free T4 and free T3 and reduced levels of thyroid stimulating hormone (TSH). Normal pregnancy ranges for each trimester have to be used.
   - Both carbimazole and prophylthiouracil (PTU) cross the placenta and high doses may cause fetal hypothyroidism and goitre, therefore, the lowest possible dose of anti-thyroid drugs should be used with monitoring of maternal thyroid function.
   - β-Blockers are safe to use for a short term if required for control of thyrotoxic symptoms.
   - Breast-feeding is safe for those on anti-thyroid treatment (PTU at or below 150 mg/day and carbimazole 15 mg/day)
   - Radioiodine therapy and diagnostic radioiodine scans are contraindicated in pregnancy; pregnancy should be avoided for at least 4 months after treatment with radioactive iodine.
   - Rarely, thyroidectomy can be performed in the second trimester.

3. Hypothyroidism
   - Hypothyroidism is caused by iodine deficiency, over-treatment of hyperthyroidism, or thyroiditis.
   - Untreated hypothyroidism has an increased rate of miscarriage, anaemia, fetal loss, pre-eclampsia and low birthweight infants.
   - Congenital hypothyroidism and cretinism in the newborn may develop.
   - Hypothyroidism is associated with postpartum depression.
   - Pregnancy probably has no major effect on hypothyroidism, and for those with adequate thyroxine replacement, pregnancy outcome is usually good.
   - The fetus is not at risk of thyrotoxicosis from maternal thyroxine replacement therapy
   - Adjustment of the dosage of thyroxine replacement is directed by thyroid function test which should be performed serially.

Immune thrombocytopenia purpura (ITP)

1. The diagnosis of ITP is one of exclusion.

2. Presentation
   - Easy bruising
   - Asymptomatic with low platelet count ($<100x10^9$/L) (slight reduction in platelet count may be due to gestational thrombocytopenia).

3. Risks
   - Fetal thrombocytopenia may occur because of transplacental passage of antibodies. Fetal intracerebral haemorrhage during labour and delivery can occur but is rare. The severity of fetal thrombocytopenia does not correlate with maternal thrombocytopenia.
   - Maternal bleeding during delivery.

4. Differential diagnosis of low platelet count in pregnancy
   - Clumping of platelets or poor sampling
   - Gestational thrombocytopenia (platelet count is usually 100-150 $x10^9$/L and asymptomatic)
   - Pre-eclampsia, HELLP (hemolysis, liver dysfunction and low platelet)
   - Drug induced
   - Viral infection, sepsis
   - DIC (dissemination intravascular coagulation)
   - Hypersplenism
   - Haemolytic uraemic syndrome (HUS)/thrombotic thrombocytopenic purpura
   - Systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS).

5. Antepartum management
   - Depends on maternal platelet count
   - Platelet count > $80x10^9$/L: serial monitoring of platelet count
   - Treatment is required in the first and second trimesters if platelet count is <20 x 10^9/L, the woman is symptomatic with bleeding or prior to a procedure like chorionic villus sampling.
   - Treatment options include steroid and intravenous immunoglobulin. Splenectomy should be avoided if possible, but may be necessary in extreme cases.
   - Anti-D immunoglobulin therapy given as an intravenous bolus for non-splenectomized rhesus-positive women may help raise platelet counts.

6. Intrapartum management
   - Possible fetal thrombocytopenia: avoid fetal scalp electrode, fetal blood sampling and instrumental delivery, avoid long and difficult labour.
   - Cord blood for platelet and then monitor neonatal platelet count for 2-5 days.

Connective Tissue Diseases

1. Systemic lupus erythematosis (SLE)
   - SLE is a chronic autoimmune disease affecting many systems: joints, skin, lung, nervous system, liver and kidneys.
   - Diagnosed by the presence of antinuclear antibodies and double stranded DNA antibodies.
   - SLE is characterized by periods of disease activity (flares) and remissions.
   - Flares are more common in pregnancy and particularly in the puerperium period (from 40% to 60%). Flares may occur at any time of the pregnancy and is more likely to occur if the disease has been active within six months of conception.
   - Risk of renal flare if lupus nephritis is not in remission or only in partial remission at conception.
   - Pregnancy complications with increased risk of: spontaneous miscarriage, intrauterine death, pre-eclampsia, preterm delivery and fetal growth restriction.
   - Adverse pregnancy outcome is related to the presence of renal involvement, hypertension, antiphospholipid antibodies (aPLs) and disease activity at the time of conception.

- For mothers with anti-Ro antibodies, there is risk of transient neonatal cutaneous lupus and fetal congenital heart block.
- Multidisciplinary care with physicians for regular monitoring of disease progress, proteinuria, hypertension and monitoring of fetal growth with antenatal ultrasound is advised.
- Low dose aspirin to prevent pre-eclampsia
- Flares should be actively managed with corticosteroids. Azathioprine, hydroxychloroquine, if indicated, should not be discontinued in pregnancy.
- Sometimes, it is difficult to differentiate superimposed pre-eclampsisa from SLE flares.
- Paediatrician should be consulted after birth because of the risks of neonatal lupus.

2. Antiphospholipid syndrome (APS)
   - APS is diagnosed when there are two or more positive readings for anticardiolipin antibodies and/or lupus anticoagulant and/or anti-β_2GP1 at least 12 weeks apart, together with history of thrombosis and/or one of the following
     - ≥ 3 consecutive miscarriages less than 10 weeks' gestation,
     - ≥ 1 fetal death at greater than 10 weeks' gestation with normal fetal morphology,
     - ≥ 1 premature birth at < 34 weeks gestation due to pre-eclampsia or severe placental insufficiency with normal fetal morphology.
   - Patients with APS may or may not have SLE.
   - There is an increased risk of severe, early onset pre-eclampsia, fetal growth restriction and placental abruption, fetal loss.
   - Antenatal aspirin with or without low molecular weight heparin is required depending on the characteristic features the patient possessed.
   - Multidisciplinary care with physicians is advised.

Epilepsy

1. In most women, pregnancy does not affect the frequency of seizures if epilepsy is well-controlled. The risk of seizure is highest in the peripartum period. All Antiepileptic drugs (AED) increase the risk of fetal malformations especially neural tube defect.

2. Pre-pregnancy
   - Optimize the control of epileptic attacks, with single agent therapy if possible. If stable, stopping AED can be tried before pregnancy (but not during pregnancy)
   - The risk is lower with monotherapy rather than polytherapy and much higher with sodium valproate.
   - Valproic acid is associated with neurodevelopmental delay and increased risk of autistic spectrum disorder and attention deficit hyperactivity disorder (ADHD) in offsprings.
   - Periconceptional folic acid supplement should be givens

3. During pregnancy
   - When generalized convulsions occur, treat as eclampsia (i.e. use MgSO4) unless proven otherwise. (e.g. early pregnancy, no proteinuria, no hypertension)
   - Free drug levels tend to fall in pregnancy and increased dosage of AED may be required.
   - Good compliance to medication is important.
   - Mid trimester fetal anomaly scan should be offered.
   - Vitamin K should be prescribed in later part of the pregnancy for mothers on enzyme-inducing AED.
   - Women should continue their AED in labour.

4. Postpartum
   - Breast feeding should not be dissuaded.
   - Contraception: Some AEDs are enzyme-inducing (phenytoin, carbamazepine, phenobarbitone, primidone) may leads to contraceptive failure when the usual oral contraceptive pills are used. Medroxyprogesterone injection and the intrauterine system (Mirena) are not affected.

Key Points

- A pre-existing disease can affect a pregnancy and vice versa.
- Maternal complications are increased during pregnancy in a woman with pre-existing medical diseases like cardiac disease or SLE.
- Fetuses can be affected by (a) uteroplacental insufficiency in diseases like SLE, APS or heart disease restriction of cardiac output, (b) transmission of antibodies like ITP, SLE or Grave's disease, (c) inheritance like congenital heart disease, (d) vertical transmission like hepatitis B, and (e) medications with teratogenicity or neonatal effects.
- Recurrence of a pre-existing medical disease like convulsion may mimic eclampsia. Flare up like lupus nephropathy may mimic pre-eclampsia.
- A multi-disciplinary team approach with joint clinic involving obstetrician, specialist physician and other professionals is helpful to provide optimal obstetric and medical management including medications.
- Pre-pregnancy counseling, prenatal diagnosis, and fetal monitoring and postnatal contraceptive advise should be provided as appropriate.

Suggested Readings

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Terms with Chinese Translation

antiphospholipid syndrome
- 抗磷脂綜合徵

asymptomatic bacteriuria - 無症狀的菌尿
fetal thrombocytopenia
- 胎兒血小板減少

gestational thrombocytopenia
- 妊娠期血小板減少症

hepatitis B - 乙型肝炎
multi-disciplinary team - 多專科小組
periconceptional folic acid - 圍孕期葉酸
pre-pregnancy counseling - 孕前諮詢
vertical transmission - 垂直傳播

Chapter 8

Multiple Pregnancies

Thomas K.O. Kou, Florrie N.Y. Yu, Kwok-yin Leung

Introduction

Multiple pregnancy refers to a pregnancy with more than one gestation, usually twin pregnancy or less commonly triplet pregnancy. It can occur after natural conception or after assisted reproduction including ovarian stimulation, intra-uterine insemination (IUI) or in-vitro fertilization (IVF). Prevalence is rising because of more widespread use of assisted reproductive techniques. Higher order multiple pregnancy (triplets or above) should be avoided by abandoning IUI cycles with too many mature follicles and limiting number (not more than two) of embryos transferred in IVF.

Type of Twins

1. Zygosity
   - Monozygotic: one zygote splitting into two embryos (identical)
   - Dizygotic: two different eggs each fertilized by a different sperm (non-identical).

2. Chorionicity and amnionicity
   - Chorionicity (number of chorions): monochorionic (one chorion), or dichorionic (two chorions)
   - Amnionicity (number of amnion): monoamniotic (one amniotic cavity), or diamniotic (two amniotic cavities).

3. Dizygotic twins are always dichorionic and diamniotic (DCDA).

4. Monozygotic twins: it depends on when the division occurs after fertilization
   - Within 72 hours (before morula forms): dichorionic diamniotic (DCDA)
   - Between the 4th and 8th day: monochorionic diamniotic (MCDA)
   - After 8th day (amnion formed): monochorionic monoamniotic (MCMA)
   - After 12th day (embryonic disk formed) and cleavage is incomplete: conjoined twins.

Prevalence

1. Monozygotic twins: 0.4% (almost constant worldwide).

2. Dizygotic twins: prevalence depends on race, heredity, maternal age, parity and use of assisted reproductive techniques.

Risks of Multiple Pregnancies

1. Multiple pregnancies are at higher risks of virtually all obstetric complications except post-term. In addition, the pregnancy symptoms are more exaggerated in mothers in twin pregnancies. The fetal and maternal risks are summarized in Table 8.1.

Table 8.1. Fetal and maternal risks in twin pregnancies

Fetal risks	Maternal risks
Perinatal mortality (around 6 times higher) Prematurity Fetal growth restriction (around 20%) Structural abnormalities (2 times higher) Difficult delivery and the associated risks (second twin)	Pre-eclampsia Gestational diabetes mellitus Anaemia Antepartum haemorrhage (placenta praevia and abruption) Caesarean section and assisted vaginal deliveries Postpartum haemorrhage Thromboembolism

2. The fetal risks in twin pregnancies were also related to the chorionicity. The monochorionic twins are at higher risks than DC twins.
   - Miscarriage: 6 times
   - Preterm delivery: 13 times for delivery < 32 weeks
   - Perinatal mortality: 2 times
   - Fetal growth restriction (FGR): 2 times
   - Fetal abnormalities: higher