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## Case 1

You are a medical student on your General Practice (GP) placement. Lily is a 30 year old female who presents to the practice with difficulty falling pregnant. Lily and her partner James have been having unprotected sexual intercourse for 2 years and have not yet fallen pregnant.

**Broadly, what are some differential diagnoses? Think about specific areas that might be affected (specific conditions are not as important for this question).**

* *Ovarian*
  + *Oligoovulation = infrequent ovulation, anovulation = no ovulation)*
  + *Including: Polycystic disorders, Hypothyroidism/hyperthyroidism, Stress, intense exercise, hyperprolactinaemia, many others!*
* *Tube*
  + *Endometriosis*
  + *Pelvic adhesions*
  + *Tubal blockage*
  + *Other tubal abnormalities*
* *Uterus*
  + *Anatomical/congenital defects*
* *Male factor infertility*
* Specific diseases are not particularly important for this question

Being the thorough Griffith medical student that you are, you take a detailed history from Lily.

Lily reports that she had her first period when she was 13 and that she never had normal periods. Due to the irregularity of her periods, she began taking the combined oral contraceptive pill when she was 16, and took this regularly, until 2 years ago, when her and James started trying to fall pregnant. Her last menstrual period was 10 weeks ago. Over the past two years, she reports having a total of 12 menstrual periods (approximately 6 per year). She has no other medical history, takes no regular medications and has no known allergies.

**How long is a normal menstrual cycle? What is the normal menstrual blood loss?**

* Normal menstrual cycles are between 21-35 days
* 30-40mL of blood loss is normal

**Define the following terms. Which of these best describes Lily’s menstrual cycle?**

|  |  |
| --- | --- |
| Amenorrhoea | Absence of menstrual periods (defined as absence for >3 cycles) |
| Oligomenorrhea | Infrequent menstrual periods (>35 days apart). **Lily has this!** |
| Polymenorrhea | Frequent menstrual periods (<21 days apart). |
| Dysmenorrhoea | Painful periods |
| Menorrhagia | Heavy menstrual bleeding |

**What is the difference between primary amenorrhoea and secondary amenorrhoea? What are common causes of each? Which does Lily have?**

* Primary amenorrhoea = failure to reach menarche (ie, never have onset of periods)
  + Often due to chromosomal irregularities (eg, Turner Syndrome) or anatomical problems
* Secondary amenorrhea = cessation of periods for 3 months / cessation of irregular menses for 6 months. Common causes include:
  + Polycystic ovarian syndrome
  + Hypothalamic amenorrhoea
  + Hyperprolactinaemia
  + Primary ovarian insufficiency

On examination, you note the following findings:

* BMI 31.4
* Acne
* Androgenic alopecia
* Hirsutism
* Acanthosis nigricans

**What is hirsutism?**

* Excessive male pattern hair growth in women (eg, chin, above upper lip, around umbilicus)
* Often idiopathic. Can be associated with excess androgens

**In light of the above findings, what is the most likely diagnosis?**

* Polycystic ovarian syndrome (PCOS)

**What are the three main overarching features of this condition?**

* Need 2 out of 3 of the following:
  + Hyperandrogenism (can be based on clinical features or laboratory tests)
  + Oligoovoulation/anovulation
  + Presence of polycystic ovaries. *Interestingly a diagnosis of PCOS is possible without the presence of ovarian cysts*
* AND rule out other causes of hyperandrogenism and anovulation

**Complete the table:**

|  |  |  |
| --- | --- | --- |
| **Type of cell:** | **Cells responds to which gonadotropin?** | **Function of these cells** |
| ***Theca cells*** | LH | Synthesise androgens |
| ***Granulosa cells*** | FSH | Via aromatase, convert androgens to oestrogens |

It is important to note that the pathophysiology of this disease is incompletely understood and the site of the primary defect is unclear.

**There are some key changes in the levels of circulating gonadotropins. Explain what the change is and why it occurs?**

* LH:FSH > 2:1
* The hypothalamus is believed to become more resistant to progesterone negative feedback = leads to increase GnRH = responds with a favoured increase in LH compared to FSH

**What happens to the levels of testosterone and oestrogen in the blood?**

* Increased LH = increased androgen production (eg, testosterone) = **elevated blood testosterone levels**
* FSH still converts androgens to oestrogen, but given there is a large increase in the amount of LH, this results in excess androgens relative to oestrogen, although **oestrogen levels are normal or slightly elevated.**

**Explain how the pathophysiology of this disease leads to each of Lily’s symptoms:**

|  |  |
| --- | --- |
| Obesity | Insulin resistance → compensatory hyperinsulinemia → obesity |
| Acanthosis Nigricans | Insulin resistance → compensatory hyperinsulinemia → epidermal hyperpigmentation and hyperplasia → hyperpigmented, velvety plaques in axilla and neck (acanthosis nigricans) |
| Anovulation | Increased LH secretion relative to FSH → increase androgen production from thecal cells in ovaries → interferes with normal follicular development → anovulation  Insulin resistance → compensatory hyperinsulinemia:   * Increased adrenal androgen production * Potentially leads to further increase in LH secretion via hypothalamus/pituitary gland * Inhibits sex hormone binding globulin production via liver = increases free tesosterone |
| Virilisation | Increased LH secretion relative to FSH → increase androgen production from thecal cells in ovaries → virilisation  And as described above too |

You won’t know and understand everything about PCOS pathophysiology, as it’s still not well understood! Understand the signs and symptoms you look for, and a basic understanding of how they are caused.

**What investigations would you like to order? Discuss why you are ordering them and how they help rule in/rule out diagnoses.**

|  |  |
| --- | --- |
| Beta-HCG | Rule out pregnancy |
| Serum LH and FSH | LH:FSH ratio > 2:1 in PCOS |
| Testosterone | Elevated |
| TFTs | Rule out thyroid disorders |
| Prolactin | Rule out hyperprolactinaemia as a cause  *Note prolactin can be mildly elevated in PCOS (mechanism not well known)* |
| Serum 17-hydroxyprogesterone | Rule out congenital adrenal hyperplasia |
| Oral glucose tolerance test | Testing for insulin resistance, often associated with PCOS |
| Fasting lipid panel | Elevated total/LDL/TG and low HDL |
| Ultrasound | May show polycystic ovaries |

**What might you think if Lily...**

|  |  |
| --- | --- |
| ...was an olympic athlete? | Increased likelihood of hypothalamus/pituitary involvement leading to ovulatory dysfunction.  *Even if in remission from anorexia nervosa, this can still cause ovulatory dysfunction* |
| ...suffered anorexia nervosa but is currently in remission? |

Given that Lily and James are trying to fall pregnant, the GP prescribe ***clomiphene***. You look up this mediation in the AMH and you find that it “inhibits hypothalamic oestrogen receptors”.

**Explain how clomiphene may provide benefit to Lily in falling pregnant.**

* Antagonises hypothalamic oestrogen receptors = blocks negative feedback of oestrogen to hypothalamus = increases pulsatile secretion of GnRH = increased FSH and LH secretion = triggers ovulation

Ten months later, you are on your ED Placement at Logan Hospital. Lily presents with vaginal bleeding and abdominal pain. The pain came on suddenly while exercising and is located in the right lower quadrant. She states that she now has had regular 28 days menstrual cycles with 4-5 day periods. However, her last normal menstrual period was 6 weeks ago.

**At this stage, what are some of your differential diagnoses?**

* Ectopic pregnancy
* Endometriosis
* Pelvic inflammatory disease
* Ovarian cyst rupture
* Adenomyosis
* Leiomyoma
* Appendicitis
* Others!

**What key test do you want to order?**

* Beta-HCG - must rule out ectopic pregnancy in any female of reproductive age with abdominal pain!

**Are there any other tests that you would like to order?**

* Abdo XR
* Bloods - FBC, U&E, LFTs
* Ultrasound scan
* Swabs to test for various STIs (for pelvic inflammatory disease)
* Others

The above tests you ordered confirm that Lily has a viable intrauterine pregnancy, but have a collection of fluid in the Pouch of Douglas (yes - it’s seen outside of the anatomy lab!)

**What is the most likely diagnosis now?**

* Ruptured ovarian cyst. Does not need treatment other than analgesia, unless hemodynamically unstable.

Now that she is pregnant, Lily has some questions about what tests she needs to have during pregnancy. Among other things, you mention some screening and diagnostic tests.

**What does the combined first trimester screening (cFTS) test involve? What does it look for?**

* These are screening tests - given to everyone (if they would like it)
  + Ultrasound - nuchal translucency measurement - to detect major chromosomal abnormalities (eg, Trisomy’s, Turner’s)
  + Maternal serum (the following are both high in Trisomy 21, other conditions)
    - Pregnancy associated plasma protein-A (PAPP-A) and
    - B-HCG

**If the cFTS is positive, what is your next step?**

* Offer diagnostic tests. These are more invasive and carry higher risk of miscarriage.
  + Chorionic villus sampling: sample placental site, then do cytogenetic testing
  + Amniocentesis: sample amniotic fluid, then cytogenetic testing

**What are the three viable autosomal Trisomies?**

* Trisomy 21 - Down’s
* Trisomy 18 - Edward’s
* Trisomy 13 - Patau

**What is non-invasive prenatal testing (NIPT)**

* Tests for fetal DNA in maternal serum. Can identify Trisomy 21, 18, 13, Monosomy X (Turner’s).
* High detection rate. Low false positives.
* Not covered under medicare - patients must pay for it

Several months later, at 33 weeks gestation, Lily presents to ED again, this time with blurred vision and right upper quadrant abdominal pain. On examination, she is found to have a blood pressure of 162/86 mmHg. She has been previously been normotensive.

**Does Lily have pre-eclampsia? Why/why not?**

* Not necessarily. A diagnosis of preeclampsia requires the following:
  + **New onset hypertensive** (>140mmHg systolic or >90mmHg diastolic) after 20 weeks gestation. Requires 2 readings, 4 hours apart **(need to repeat the reading for Lily)**
  + AND at least one of the following:
    - Proteinuria
    - End organ dysfunction (renal insufficiency, liver involvement, neurological involvement, haematological complications)
    - Foetal growth restriction
  + We don’t know if she proteinuria or end organ dysfunction or foetal growth restriction (need to investigate)
* Other differentials might include
  + Pre-existing (chronic) hypertension - although not for Lily in this case
  + Gestational hypertension
  + Severe pre-eclampsia (>160/100)
  + White coat hypertension

**What causes preeclampsia?**

* Not completely understood but believed to be due to fibrosis of placental blood vessels. This can lead to systemic problems causing vascular damage.

**What investigations would you like to order?**

* Urine dipstick (looking for protein in urine)
* FBC (looking for low platelets)
* eGFR and creatinine (assess renal function)
* LFTs (looking for elevated transaminases, suggesting liver involvement)
* Others

**What is eclampsia?**

* Onset of seizures in a woman with pre-eclampsia - before during or after delivery.

**What is the HELLP syndrome?**

* Occurs during 10-20% of (pre)eclampsia cases.
* Cause it not well known, but related to thrombi formation in the vasculature, leading to:
  + **H**aemolysis - haemolytic anaemia (RBCs undergo haemolysis)
  + **E**levated
  + **L**iver enzymes
  + **L**ow
  + **P**latelets (thrombocytopenia)

Further investigations confirm that Lily has elevated levels of protein in her urine, elevated creatinine and elevated aminotransferases (AST and ALT). She also has elevated ALP. Repeat blood pressure measurements are 154/86 mmHg and 155/83 mmHg.

**Why is her ALP elevated?**

* ALP is produced by the placenta during pregnancy.

**What medication might you prescribe to Lily to control her blood pressure? Explain the MOA.**

* Appropriate antihypertensives for pregnancy include:
  + Labetalol (non-selective beta blocker)
  + Methyldopa (a2 agonist)
  + Nifedipine (dihydropyridine calcium channel blocker)
* ACE inhibitors and Angiotensin Receptor Blockers are contraindicated during pregnancy as they are teratogenic

**What if… Lily presented to ED at 32 weeks gestation stating ‘her waters had broken’ and uterine contractions. If the following drugs were prescribed, what would be the rationale for in providing these?**

* Note: This is preterm premature rupture of membrane (PPROM) - the rupture of membranes before 37 weeks gestation. Note that this is different to premature rupture of membranes (PROM) which is defined as the rupture of membranes prior to the onset of uterine contractions
* Plan for delivery >34 weeks

|  |  |
| --- | --- |
| Betamethasone | Can be given from 24-34 weeks gestation to accelerate fetal lung maturity and increase surfactant production to improve outcomes/prevent respiratory distress |
| Salbutomol | Agonist of beta2 receptors → tocolytic → relax uterus → delay labour |
| Nifedipine | Calcium channel blocker → tocolytic → relax uterus → delay labour |
| Amoxicillin with clavulanic acid | As prophylaxis for infection. Remember that the amnion is usually protecting the fetus from infection. |

In actual fact, Lily presents to the hospital at 38 weeks with uterine contractions.

**What are the three stages of labour?**

* Stage 1 - dilation and effacement of cervix to 10cm
* Stage 2 - delivery of baby
* Stage 3 - delivery of placenta

Lily has an uncomplicated birth. After 10 hours a baby boy, Harry is born. You are asked to assess Harry at 1 and 5 minutes of age.

**Fill out the following table to explain the APGAR score.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Stands for...** | **Score 2** | **Score 1** | **Score 0** |
| **A** | Appearance | Pink | Extremities blue | Pale/blue |
| **P** | Pulse | >100bpm | <100bpm | Absent |
| **G** | Grimace | Cries and pulls away | Grimaces or weak cry | No response to stimulation |
| **A** | Activity | Active movement | Arms, leg flexed | No movement |
| **R** | Respiration | Strong cry | Slow, irregular | No breathing |

## Case 2

**You are a third year medical student on your Women’s Health rotation at Sunshine Coast University Hospital. You have been asked to see two patients in the general gynaecology outpatient clinic today!**

Your first patient, Monica, is 65 years old and presents with vaginal bleeding. She describes the bleeding as being scant. Menarche was at age 10 and she went through menopause at age 57. She used oestrogen hormone replacement therapy for the first 3 years following menopause, but has not used it recently. She has never had an abnormal cervical screening test or pap smear.

**What are your differential diagnoses?**

* *Hormone (oestrogen) therapy*
* *Atrophy of vagina or endometrium*
* *Uterine or cervical polyps*
* *Endometrial hyperplasia*
* *Cancer of endometrium, cervix or vagina*
* *Others*

*Note that the PALM-COEIN acronym is for abnormal uterine bleeding in women of* ***reproductive******age*** *(not in this case!).*

* P - polyps
* A - adenomyosis
* L - leiomyoma (uterine fibroids)
* M - malignancy and hyperplasia
* C - coagulopathies
* O - ovulatory dysfunction
* E - endometrial cancer
* I - idiopathic
* N - not otherwise specified

**What is the most common cause of post-menopausal bleeding?**

* Vaginal or endometrial atrophy

**What diagnoses must not be missed?**

* Cancer - often endometrial (but can be of cervix or vagina)
* All post-menopausal bleeding MUST be investigated! Cancer until proven otherwise!m Need to rule it out!

**What risk factors for the not to be missed conditions do you want to ask about when taking a medical history from these patients? Explain why they are risk factors.**

Risk for endometrial cancer (these are conditions associated with **increased/prolonged oestrogen exposure**)

* Nulliparity (progesterone is main hormone of pregnancy)
* Early menarche / late menopause
* obesity e.g. diabetes
* PCOS (due to the obesity AND the anovulatory cycles)
* Unopposed (without progesterone) oestrogen replacement therapy (eg, for menopausal symptoms)
* Breast cancer - history of breast cancer, tamoxifen treatment (has anti-oestrogenic effects at breast, but oestrogenic effects in uterus)

**What examinations do you want to perform?**

* Abdominal examination (look for abdominal masses)
* Speculum examination (assess for atrophic vaginitis, tumours of cervix/vagina/vulva, cervical polyps)
* Bimanual examination (assess uterine size/mobility/position, cervical/vaginal masses, adnexal masses)

**What are the key investigations that will help you rule out the not to be missed diagnosis?**

* Gold standard: endometrial biopsy + histology (can be done as part of pelvic exam)
* Transvaginal ultrasound (can assess endometrial thickness) - doesn’t give definitive diagnosis
* Other imaging (eg, abdominal USS, CXR, CT) → looking for metastasis
* Not key for diagnosis - but FBC and coags to assess for anaemia or other causes

**How might a family history of colorectal cancer affect your consideration of your provisional diagnosis?**

* Increased chance of endometrial cancer
* Hereditary nonpolyposis colorectal (Lynch syndrome) is an inherited cancer syndrome, that predisposes family members to certain cancers including **colorectal** and **endometrial**

**What if Monica presented with spotting while taking hormone replacement therapy (oestrogen and progesterone) . How might this affect your differential diagnosis?**

* Potentially due to the hormone replacement therapy / less likely to be hyperplasia or malignancy.
* Although should still be investigated.

**What do the following tumour markers represent?**

|  |  |
| --- | --- |
| **Tumour marker** | **Elevated in which cancers?** |
| CA 19-9 | Pancreatic |
| CA-125 | Ovarian |
| CEA | Bowel (among many others) |

Your second patient, Rachel, is 42 years old and has been referred to the gynaecologist from her GP, following an abnormal routine cervical screening test. She is asymptomatic. She is a smoker and has a history of unprotected sexual intercrouse with multiple sexual partners.

**What are some risk factors for cervical cancer?**

* Early onset sexual activity / multiple sexual
* Immunosuppression (eg, HIV)
* Cigarette smoking
* History of STIs
* Potential risk factors (correlation, but not necessarily causation)
  + Low SES
  + Oral contraceptive use
* suspect in patients who haven’t had pap smears/CST done!

**If Rachel has cervical cancer, but had presented with symptoms, what might those symptoms be?**

* Abnormal vaginal bleeding (postcoital spotting, intermenstrual bleeding/irregular vaginal bleeding)
* Abnormal vaginal discharge (blood stained or purulent malodorous discharge)
* Late symptoms: tumour spread to vagina, bladder, rectum etc
  + Swelling in lower extremities (due to compression of veins)
  + Lymphadenopathy
  + Other signs of metastatic disease

**What does the cervical screening test look for? What did the pap smear look for and what is the difference?**

* Presence of HPV (looking for the virus)
  + 16 and 18 are the high risk viruses, most likely to progress to cancer
* May then look at cytology (eg, if HPV is present - see next question)
* Pap smear was only cytology based (looking for abnormal cells) - the CST also looks for the virus!!!

**What are the four possible test results? What is the appropriate management in each case?**

|  |  |
| --- | --- |
| **Test Result** | **Appropriate Management (describe briefly)** |
| HPV not detected | Return to screening in 5 years |
| HPV detected (but not types 16 or 18) | Reflex LBC → depending on the cytology  Negative or LSIL → repeat HPV in 12 months  HSIL → referral to gynaecologist (for **colposcopy**)  (for more details, see flowchart in link below) |
| HPV (16/18) detected | Reflex **LBC** AND referral to gynaecologist (for **colposcopy**)   * Refer to gynae regardless of cytology result |
| Unsatisfactory HPV test | Repeat 6-12 weeks |

\*LBC = liquid based cytology.

\*\*Reflex liquid based cytology is when the same liquid sample collected for the initial HPV test is then used by the lab to perform a cytology.

Look up more info here. Important for DHC and DKHI! <http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/healthcare-providers>

**BONUS QUESTION (this is beyond Year 2 level, but interesting). How would the cervical screening test process change if a woman presented with intermenstrual or post-coital bleeding?**

* Order a co-test! This means both the HPV test and liquid based cytology are performed at the same time, regardless of the result of the HPV test!