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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 (most common cause of infertility in females)*
 - *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 (26%)*
- *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? In what way is Lily's menstrual cycle abnormal?

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

Define the following terms.

Amenorrhoea	Absence of menstrual periods (defined as absence for >3 cycles)
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Dysmenorrhoea	Painful periods
Menorrhagia	Heavy menstrual bleeding

NB: Modern O/G is moving away from the use of some of these terms (e.g. menorrhagia, metrorrhagia, menometrorrhagia) and using clearer, simpler language e.g. heavy menstrual bleeding, abnormal uterine bleeding etc. Maybe don't learn the weird ones.

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 amenorrhoea = 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
- 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)
 - Oligoovulation/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 e.g. Cushing's disease, congenital adrenal hyperplasia

Complete the table:



Type of cell:	Cells responds to which gonadotropin?	Function of these cells
<i>Theca cells</i>	LH	Synthesise androgens
<i>Granulosa cells</i>	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	<p>Increased LH secretion relative to FSH → increase androgen production from thecal cells in ovaries → interferes with normal follicular development → anovulation</p> <p>Insulin resistance → compensatory hyperinsulinemia:</p> <ul style="list-style-type: none"> ➢ 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 testosterone
Virilisation	Increased LH secretion relative to FSH → increase androgen production from thecal cells in ovaries → virilisation



	And as described above too
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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 <i>Note prolactin can be mildly elevated in PCOS (mechanism not well known)</i>
Serum 17-hydroxyprogesterone	Rule out congenital adrenal hyperplasia (21-hydroxylase deficiency – the main one)
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. <i>Even if in remission from anorexia nervosa, this can still cause ovulatory dysfunction</i>
...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 medication 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



- Appendicitis
- Ovarian cyst rupture
- Ovarian torsion
- Pelvic inflammatory disease/tubo-ovarian abscess
- 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?

- Bloods - FBC, U&E, LFTs, beta-hCG
- urinalysis
- Ultrasound scan - transabdominal and transvaginal
- STI testing
- Others

The above tests you ordered confirm that Lily has a viable intrauterine pregnancy, but has 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 supportive care, 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 (10-13 weeks): sample placental site, then do cytogenetic testing
 - Amniocentesis (>15 weeks): 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 free foetal 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