# check

RACGP CPD solution

Unit 601
January–February 2023

# Iron deficiency

RACGP

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# Iron deficiency

**Unit 601 January–February 2023**


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- Communication skills and the patient–doctor relationship
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## About this activity

Iron deficiency is a common health issue in Australia, with anaemia affecting approximately 8% of children aged <5 years, 15% of non-pregnant premenopausal women and 12% of pregnant women.[1] Consequently, iron deficiency is an important diagnosis to consider for patients presenting to general practitioners with symptoms such as fatigue and pallor.

Although there are no Australian prevalence estimates for iron deficiency in infants and toddlers, a 2022 study found that approximately 90% of infants aged 6–11.9 months and 25% of toddlers aged 1–2 years had inadequate iron intake.[2]

Iron requirements increase during adolescence, and women are particularly susceptible to iron deficiency because of menstrual blood loss.[3] The Australian Bureau of Statistics has reported that 40% of girls aged 14–18 years have inadequate iron intake to meet physiological demands.[4]

Iron demand increases three-fold during pregnancy, reaching a peak in the third trimester. In total, 1000–1200 mg of iron is required.[5] Iron deficiency rates of almost 20% during pregnancy have been reported in some Australian studies.[5]

Heavy menstrual bleeding (HMB) is the most common presentation of abnormal uterine bleeding in premenopausal women in the general practice setting, affecting 25–30% of women of reproductive age.[6] Continued HMB results in a high risk of developing iron deficiency anaemia.

Inflammatory bowel disease (IBD) affects >80,000 Australians, and it is predicted that one in 200 Australians will develop IBD.[7] Patients with IBD often have iron deficiency anaemia due to both chronic blood loss and impaired iron absorption.[8]

This edition of *check* considers the investigation and management of iron deficiency in general practice.

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## Learning outcomes

At the end of this activity, participants will be able to:

- list the factors that increase the risk of iron deficiency in infancy and adolescence
- outline the potential causes of abnormal uterine bleeding in premenopausal women
- discuss iron demand in pregnancy, highlighting major routes of loss and gain
- describe the additional factors that must be considered when considering ferritin levels in a patient with inflammatory bowel disease.

## Authors


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## Abbreviations

| | |
|---|---|
| **AUB** | abnormal uterine bleeding |
| **BMI** | body mass index |
| **COEIN** | Coagulopathy, Ovulatory, Endometrial, Iatrogenic or Not yet classified |
| **CRP** | C-reactive protein |
| **ESR** | erythrocyte sedimentation rate |
| **FIGO** | International Federation of Gynecology and Obstetrics |
| **Hb** | haemoglobin |
| **HMB** | heavy menstrual bleeding |
| **IDA** | iron deficiency anaemia |
| **LNG-IUS** | levonorgestrel intrauterine system |
| **PALM** | Polyps, Adenomyosis, Leiomyoma (fibroids), Malignancy or hyperplasia |
| **PCOS** | polycystic ovary syndrome |
| **TPA** | tissue plasminogen activator |
| **TXA** | tranexamic acid |
| **WHO** | World Health Organization |

CASE

# 1 Jack is unusually pale

Jack is a previously healthy boy, aged 18 months, who is brought in by his mother, Annie. Annie is upset and worried something is wrong after her sister commented on how pale Jack is.

## Question 1

What history would you seek from Jack's mother, Annie?

### Further information

Annie tells you that Jack is a fussy eater. He likes eggs, fruit and vegetables but is not keen on meat or fish. He drinks a 300 mL sippy cup of cow's milk with each meal, totaling three 300 mL cups per day. Annie tells you that her sister has been diagnosed with coeliac disease, although Jack does not have any abdominal symptoms to report and has reached his developmental milestones. There is no personal or family history of abnormal bleeding.

## Question 2

What would you look for on examination?

### Further Information

On examination, Jack's height, weight and head circumference are on the 50th percentile and following the growth curve closely. His skin and conjunctiva appear pale, but there is no scleral icterus. His heart rate is regular; however, he does have a soft systolic murmur on auscultation. There is no lymphadenopathy or hepatosplenomegaly on abdominal examination.

## Question 3

What is your differential diagnosis for a pale child?

### Further information

You request some blood tests to investigate your suspicion of iron deficiency. Jack's results are shown in Table 1.

**Table 1. Jack's blood test results**

| | Result | Reference Range |
|---|---|---|
| Haemoglobin concentration | 67 g/L | 110–145 g/L |
| White cell count | 8.95 × $10^9$/L | 5.0–17.0 × $10^9$/L |
| Platelet count | 762 × $10^9$/L | 150–400 × $10^9$/L |
| Red cell count | 4.46 × $10^{12}$/L | 3.9–6.0 × $10^{12}$/L |
| Haematocrit | 0.25 L/L | 0.34–0.44 L/L |
| Mean cell volume | 56 fL | 72–87 fL |
| Mean cell haemoglobin | 15 pg | 24–32 pg |
| Mean cell haemoglobin concentration | 267 g/L | 320–360 g/L |
| Red cell distribution width | 21.2% | 9–15% |
| Mean platelet volume | 8 fL | 8–12 fL |
| Neutrophils | 5.79 × $10^9$/L | 1.5–8.5 × $10^9$/L |
| Lymphocytes | 0.91 × $10^9$/L | 1.5–9.5 × $10^9$/L |
| Monocytes | 0.15 × $10^9$/L | 0.2–1.0 × $10^9$/L |
| Eosinophils | 0.03 × $10^9$/L | 0.0–0.8 × $10^9$/L |
| Basophils | 23.1 × $10^9$/L | 0.0–0.2 × $10^9$/L |
| Ferritin | 6 µg/L | 20–100 µg/L |
| Serum iron | 2 µmol/L | 5–25 µmol/L |
| Transferrin saturation | <2% | 10–45% |

## Question 4

How would you interpret Jack's blood test results?

**Further information**

You diagnose Jack with iron deficiency anaemia.

## Question 5

How would you manage Jack?

# CASE 1 Answers

## Answer 1

It is recommended to begin by asking about perinatal history, including gestational age, birth weight, previous pregnancies, pregnancy complications and blood loss. It is also important to enquire about maternal history of iron deficiency and conditions that might put Annie at risk of iron deficiency, such as a restricted diet.

Annie should be asked about other symptoms she may have noticed, such as changes in sleep patterns to suggest increased fatigue, intake of non-food items (pica), irritability, fevers, weight loss or bone pain. Sometimes enquiring about the onset of pallor can be helpful information to ascertain to guide the differential diagnosis.

A personal or family history of abnormal bleeding or known bleeding disorders should be noted. Annie should be asked specifically about any bleeding from gums, evidence of bleeding into muscles or joints, abnormal or easy bruising, heavy menstrual bleeding or postpartum haemorrhage, or any bleeding following procedures.

Finally, a detailed history of Jack's dietary intake should be taken, including the quantity, frequency and duration of breast and/or bottle feeds; type and amounts of solids that have been introduced; volume of cow's milk consumed and when it was introduced. Any gastrointestinal symptoms that may occur following food should be noted (eg abdominal pain, bloating or diarrhoea).

## Answer 2

A complete physical examination is recommended, including Jack's weight, height and head circumference (which should be plotted on his growth chart), as well as his expected size based on parental height. An inspection of the conjunctivae, sclera and skin helps evaluate for pallor or jaundice. Further examination should include palpation of lymph nodes; abdominal examination to assess for any organomegaly; and cardiovascular examination, noting heart rate and presence of murmurs.

## Answer 3

Pallor in a child could be due to anaemia secondary to haematological or solid organ malignancy, haemoglobinopathies or red cell membrane disorders or, more commonly, nutritional deficiencies. Given Jack's history and examination, the most likely cause of anaemia is iron deficiency secondary to diet. Iron deficiency occurs when iron demands or losses exceed iron intake and/or absorption and is often multifactorial. Young children are at risk of iron deficiency as a result of several mechanisms.[1,2]

**Increased iron requirements**

- Catch-up growth in children born premature or with low birth weight
- Growing infants, children and adolescents have increased dietary iron requirements when compared with adults

**Inadequate iron supply**

- Prematurity, perinatal haemorrhage or maternal iron deficiency
- Vegan or vegetarian diet
- Late introduction of iron-rich solids
- Exclusive breastfeeding past six months of age
- Early introduction (<12 months of age) of cow's milk

**Excessive blood loss and/or malabsorption**

- Gastrointestinal conditions
  - Gastroesophageal reflux

  - Cow's milk protein intolerance
  - Meckel's diverticulum
  - Inflammatory bowel disease
  - Coeliac disease
  - Infection (eg intestinal parasites such as hookworm and other helminths)
  - Intussusception
- Excessive bleeding, including that secondary to underlying bleeding disorders
  - von Willebrand disease
  - haemophilia.

Where symptomatic, iron deficiency in young children often manifests with non-specific symptoms such as irritability, fatigue and pallor, with the latter being the most common presentation of iron deficiency in children. The ability of children to physiologically compensate for anaemia often results in a lack of apparent symptoms until the anaemia has become more severe. Patients with severe anaemia may present with cardiomegaly, decreased appetite and tachyponea. Pica, an intense craving for non-food items, is common and specific for iron deficiency. Iron deficiency in children is associated with impaired neurocognitive development and restless legs.

## Answer 4

Jack has iron deficiency anaemia. A low ferritin result is diagnostic of iron deficiency, but a normal ferritin result does not rule out iron deficiency, especially in the setting of inflammation. In infants and children, a ferritin result of <20 μg/L is indicative of inadequate iron stores.[1,3] Reactive thrombocytosis is often seen in patients with iron deficiency anaemia.[4]

## Answer 5

It is important to determine and treat the underlying cause of the iron deficiency. In Jack's case, it appears that he is consuming too much cow's milk. Cow's milk has low iron content and bioavailability, with excessive consumption leading to children eating fewer iron-containing foods. Furthermore, cow's milk interferes with iron absorption from other foods and can lead to occult intestinal blood loss. To address this, Jack's mother should decrease his milk intake to <500 mL of cow's milk per day.

To avoid iron deficiency, infants should have an iron-rich diet from six months of age and should not consume cow's milk until they are 12 months of age, with a maximum of 600 mL of cow's milk per day.[5] Breastmilk has a low iron content but high bioavailability. For infants who are breastfed, introduction of iron-fortified foods, commonly cereals, can be given from six months of age. Iron-fortified formula typically provides adequate iron intake; however, formula-fed infants may be at increased risk of iron deficiency with the transition from formula to cow's milk.[6]

To correct the iron deficiency, Jack should be given oral iron replacement at a dose of 3 mg/kg/day.[1] A liquid iron preparation containing 6 mg/mL of elemental iron would be a good option for replacing iron in this case.[1] Milk and other dairy products should be avoided for at least one hour prior to consuming oral iron and for two hours after. A refractory response to oral iron preparations or an inability to tolerate the preparations would indicate the consideration of intravenous iron treatment.

## Resources for doctors

- BloodSafe eLearning – Paediatric: Iron deficiency anaemia learning course, https://learn.bloodsafelearning.org.au/course/about/neonatal-paediatrics-ida

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CASE

# 2 Jeongyeon is struggling in school

Jeongyeon, aged 15 years, is a student who presents with persistent tiredness for the past six months. She finds classes after lunch challenging and feels increasingly anxious about underperforming at school. She no longer plays sport, and her mother feels that she is becoming increasingly withdrawn. Jeongyeon admits she has been feeling emotionally low; however, she has not had any thoughts or acts of self-harm.

## Question 1

What factors could potentially be causing Jeongyeon's symptoms?

### Further information

You suspect Jeongyeon may have iron deficiency as the mostly likely diagnosis because of her recent growth spurt. There have been no family or external stressors, and her parents report her to be a happy and sociable child.

## Question 2

What further clinical history would you seek?

### Further information

Jeongyeon does not report symptoms such as shortness of breath, chest pain or heart palpitations. On specific questioning, her periods last five days with no flooding or clots. She does not report any bleeding manifestations and underwent a tonsillectomy at the age of four years without complication. Pregnancy is excluded.

Jeongyeon adopted a vegetarian diet approximately one year ago on ethical grounds after taking part in Veganuary. At the time she did some online research into the best plant-based sources of iron. She is not taking any regular medications, her weight is stable, she does not smoke or drink alcohol and does not report any additional family medical history. On closer questioning, she confesses to chewing ice for the past couple of months.

## Question 3

Which factors are contributing to Jeongyeon's symptoms?

## Question 4

What initial investigations would you consider?

### Further information

Jeongyeon's blood tests are shown in Table 1.

**Table 1. Jeongyeon's blood test results**

| | Result | Reference range |
|---|---|---|
| Haemoglobin concentration | 121 g/L | 120–150 g/L |
| White cell count | 7.03 × $10^9$/L | 4.2–11.2 × $10^9$/L |
| Platelet count | 379 × $10^9$/L | 135–400 × $10^9$/L |
| Red cell count | 4.41 × $10^{12}$/L | 3.73–5.15 × $10^{12}$/L |
| Haematocrit | 0.408 L/L | 0.35–0.45 L/L |
| Mean cell volume | 84 fL | 83.5–99.5 fL |
| Mean cell haemoglobin | 30 pg | 27.5–33.1 pg |
| Mean cell haemoglobin concentration | 328 g/L | 315–350 g/L |
| Red cell distribution width | 15.9% | 10.0–15.9% |
| Mean platelet volume | 9.1 fL | 7–13 fL |
| Neutrophils | 3.79 × $10^9$/L | 2.0–7.1 × $10^9$/L |
| Lymphocytes | 2.45 × $10^9$/L | 1.1–3.6 × $10^9$/L |
| Monocytes | 0.4 × $10^9$/L | 0.3–0.9 × $10^9$/L |
| Eosinophils | 0.25 × $10^9$/L | 0.0–0.5 × $10^9$/L |
| Basophils | 0.04 × $10^9$/L | 0.0–0.1 × $10^9$/L |
| Ferritin | 9 µg/L | 20–120 µg/L |
| Serum iron | 8 µg/L | 5–30 µg/L |
| Transferrin saturation | 12% | 10–45% |
| C-reactive protein | 1.3 mg/L | 0.0–3.0 mg/L |

## Question 5

How would you interpret these results?

## Question 6

What would be your initial management plan?

## Question 7

When would you next review Jeongyeon?

## Question 8

What would be your longer-term management plan for Jeongyeon?

## CASE 2 Answers

### Answer 1

Jeongyeon's reported symptoms of fatigue, headaches, poor concentration and mood disturbances warrant further exploration.[1] The differential diagnosis is broad and includes (but is not limited to):

- lifestyle factors, such as physical inactivity or poor sleep
- endocrine disorders, including thyroid disorders or diabetes
- psychological factors, including anxiety, depression or emerging eating disorders
- nutritional disorders, such as deficiencies in iron, folate or vitamin B12.

A second period of rapid growth and development occurs in adolescence and is associated with an increased iron demand. External pressures can lead to dietary changes, including restrictive diets. Females experience a greater iron loss in adolescence through the onset of menses. With these factors combined (ie increased iron demand, potential poor iron intake and increased iron loss), female adolescents are particularly susceptible to iron deficiency, with an estimated prevalence of 13% of this subpopulation being iron deficient.[2]

While anaemia is the most recognised presentation of iron deficiency, iron deficiency in the absence of anaemia is associated with symptoms of fatigue, poor concentration and decreased physical performance and productivity. Correction of iron deficiency has been shown to improve the accuracy with which both simple and complex cognitive tasks are performed.[3] Iron-dependent enzymes are necessary for the synthesis, function and degradation of neurotransmitters such as dopamine, serotonin and noradrenaline. It is through this pathway that iron deficiency is thought to affect mood and has been shown to be associated with depression in both adolescents and adults.[4]

### Answer 2

Iron deficiency can be a manifestation of an underlying medical condition and is often multifactorial. Risk factors can be divided into physiological, environmental or pathological. A detailed medical history should include symptoms suggestive of food intolerances such as abdominal pain, bloating and diarrhoea, which are suggestive of coeliac disease.

Jeongyeon's history of the onset of menarche and any symptoms suggestive of heavy menstrual bleeding (HMB) should be explored and an inherent bleeding disorder (eg factor deficiency or von Willebrand disease) considered if Jeongyeon has had heavy periods since the onset of menarche, a history of nosebleeds or family history of the same.

Any change in Jeongyeon's diet should be explored, particularly the avoidance of meat, along with her symptoms. While Jeongyeon reported rather generic symptoms of fatigue, poor concentration and mood disturbances, you should ask about further symptoms suggestive of iron deficiency, including 'air hunger', heart palpitations, dizziness and specific symptoms of pica (a desire to eat non-foodstuffs) such as ice, paper or soil, which can be seen in severe iron deficiency.

### Answer 3

Jeongyeon's vegetarian diet in the context of recent growth and development is the greatest risk factor for the development of iron deficiency with or without anaemia. She does not report any gastrointestinal symptoms to suggest malabsorption. A detailed menstrual history excludes HMB and, combined with an uneventful tonsillectomy, makes an underlying inherited bleeding disorder very unlikely.

Dietary iron is available in two forms: haem iron, which is found in animal sources (red meat and, to a lesser extent, poultry and fish), and non-haem iron, which is the only form of iron available in plant-based sources (nuts, cereals, beans and vegetables – particularly leafy greens). Approximately 25% of haem iron is absorbed, compared with only 10% of non-haem iron.[5] Dietary iron absorption is enhanced by vitamin C and inhibited by calcium, tannins and certain medications (eg proton pump inhibitors).

It is recommended that adolescent females consume 15 mg of iron/day, compared with 11 mg/day for their male counterparts.[6] While it is possible to achieve this with a vegetarian or vegan diet, individuals must be cognisant of iron-rich plant-based alternatives.

### Answer 4

Blood tests would be required to confirm iron deficiency. These should include a full blood examination, ferritin, transferrin saturation and C-reactive protein (CRP).

### Answer 5

Jeongyeon's haemoglobin concentration is not diagnostic of anaemia, which the World Health Organization (WHO) defines as a haemoglobin concentration <120 g/L in women.[7] This criterion was created by assessing the haemoglobin concentration distribution in healthy population groups, despite a large variation is haemoglobin concentration and regardless of 10–14% of women being iron deficient.[8] This may account for the variations observed in reference ranges between laboratories for haemoglobin concentration and serum ferritin and haemoglobin concentration. Indeed, in the recent cross-sectional study of 25,880 women,[9] excluding those with iron deficiency (defined as ferritin <12 μg/L) resulted in a shift in the average haemoglobin levels by an average of 10 g/L.

Jeongyeon does have iron deficiency, defined as a ferritin result of <15 μg/L by the WHO; however, recent large population studies suggest that iron deficiency may be present at ferritin levels of <20 μg/L in children or <25 μg/L in adult women.[10] Current opinion suggests that ferritin <15 μg/L is iron deficiency, while ferritin <30 μg/L is iron depletion.[11,12]

Ferritin is the principle iron storage protein and a specific test for iron deficiency; however, as it is an acute phase reactant (ie ferritin will be elevated in the setting of acute disease, chronic inflammation and chronic disease), it is not particularly sensitive in disease or illness. Iron studies should be deferred to the convalescent stage of an acute illness or CRP ordered concurrently, with higher ferritin thresholds considered if CRP is elevated. Transferrin saturations and serum iron can be variable during the course of the day and in response to diet but are low in the presence of iron decficiency.[13]

Looking at Jeongyeon's blood results, her full blood examination reveals a haemoglobin concentration at the lower end of normal with relatively small cells (mean cell volume also at the lower end of normal) and a marginally elevated red cell distribution width (reticulocytes are larger). These infer likely development of microcytic anaemia and are supported by a low serum ferritin and low transferrin saturations. Together this reflects significant iron deficiency without anaemia (at present).

## Answer 6

Nutritional education can be provided to help improve iron intake; however, dietary modification alone is inadequate for correcting the deficiency. Oral iron is first-line therapy, with intravenous iron reserved for those who require rapid restoration of iron (due to moderate-to-severe anaemia or emergent surgical intervention) or where the patient is intolerant or refractory to oral iron. It is important to ensure the prescribed oral iron preparation contains an adequate amount of elemental iron. Evidence suggests that alternate-day dosing results in similar levels of iron absorption while limiting side effects, predominantly gastrointestinal.[14] To maintain a suitable iron dose while limiting gastrointestinal side effects, a dose of 65 mg of elemental iron is recommended on alternate days.[15] Dairy, tea and coffee products can limit absorption so should not be consumed around the time of iron ingestion.

## Answer 7

Follow-up after 2–4 weeks is important to identify and troubleshoot any side effects of the oral iron tablets and to assess haemoglobin response to oral iron, with an adequate response defined as an increase in haemoglobin of 10–20 g/L.[16] If the patient has iron deficiency without anaemia, repeat testing is not indicated at this time.

If the patient is tolerating and responding to oral iron, then treatment should continue for a further three months or until haemoglobin concentration has normalised. If the patient is iron deficient but not anaemic, repeat iron studies should be performed after three months of iron replacement. If side effects are experienced or there is evidence of an inadequate response to oral iron, then intravenous iron should be administered. The dosing of intravenous iron has been traditionally calculated using the Ganzoni equation below. However, a more pragmatic proposal would be 10–20 mg/kg depending on the severity of iron deficiency.

Total iron deficit = weight (kg) × (target haemoglobin – actual haemoglobin in g/L) × 2.4 + iron stores (mg).

For example, a patient with a body weight of 60 kg, a haemoglobin concentration of 80 g/L and a target haemoglobin concentration of 130 g/L. The total required iron dose would be calculated as:

(60 x [130 – 80]) × 0.24 + 500 mg = 1220 mg.

Pragmatically, this may be an initial dose of 1000 mg, as the preparations are available in 1000 mg vials and the maximal dosing in Australia in one sitting is currently 1000 mg.

## Answer 8

If risk factors for iron deficiency persist, as is the case for Jeongyeon, then the possibility of recurrence is high when iron replacement is ceased. For those who have tolerated and responded to oral iron, the focus can switch to iron supplementation once iron levels are replete. This could be in the form of lower daily dosing of elemental iron (20 mg/day) or continuing the same formula at a reduced frequency (1–2 times/week). If the patient required an iron infusion, this supplemental strategy can still be considered as tolerance is often improved with lower doses of oral iron and should be implemented as ferritin approaches the lower end of the normal range.

If the patient received intravenous iron as a result of being refractory or unable to tolerate all forms of oral iron, then iron studies should be monitored 3–6 monthly; however, the patient should be encouraged to bring forward their follow-up bloods tests if they experience a recurrence of their symptoms. Further intravenous iron should be administered once iron deficiency is diagnosed.

## Conclusion

Iron deficiency in adolescence is common and can present with cognitive and behavioural symptoms. As well as addressing the aetiology of iron deficiency, defined treatment courses may be required, with regular iron supplementation or close monitoring with subsequent infusions.

## Resources for doctors and patients

- Nutrition Australia – Iron fact sheet, https://nutritionaustralia.org/app/uploads/2020/05/Iron-2014-1.pdf

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CASE

# 3 Virginia has heavy periods

Virginia, aged 40 years, works full time as a manager at a retail firm. She reports that her periods have become noticeably heavier over the past six months, with frequent flooding that causes her significant embarrassment. Prior to this, she had been well with normal, regular periods. She reports that over the past few months she has been feeling tired most of the time and occasionally feeling breathless. Virginia has three teenage children, with her youngest child delivered 12 years ago by elective caesarean section for placenta praevia, at which time she underwent tubal occlusion with clips.

## Question 1

What history would you seek from Virginia?

### Further information

Virginia explains that her menstrual cycles are regular, occurring every 27 days. Her periods typically last for seven days and are particularly heavy on the first 3–5 days, with significant clotting and flooding. Despite using tampons and extra-large sanitary pads, she must change the products 2–3 times overnight to avoid leaking. She has no pain associated with her periods, and her cervical screening test last year was negative.

## Question 2

What would you look for in your examination of Virginia, and how would you assess her menstrual loss?

### Further information

Virginia's body mass index (BMI) is 25 kg/m$^2$ and she displays no sign of hirsutism. She is not taking any medication, and there is no family history of any bleeding disorders. Abdominal examination reveals no mass, and bimanual examination does not show any evidence of tenderness, uterine or adnexal abnormality.

## Question 3

What would you consider are the likely causes of Virginia's menstrual problem?

### Further information

In view of Virginia's history and examination, a provisional diagnosis of heavy menstrual bleeding (HMB) is made. As an initial assessment, it would be appropriate to order simple investigations to exclude iron deficiency and anaemia with serum ferritin and a full blood examination.

The results of Virginia's blood tests are shown in Table 1.

**Table 1. Virginia's blood test results**

| | Result | Reference range |
|---|---|---|
| Haemoglobin concentration | 109 g/L | 115–135 g/L |
| White cell count | 6.62 × $10^9$/L | 3.0–10.0 × $10^9$/L |
| Platelet count | 338 × $10^9$/L | 150–400 × $10^9$/L |
| Red cell count | 5.31 × $10^{12}$/L | 3.95–5.15 × $10^{12}$/L |
| Haematocrit | 0.42 L/L | 0.33–0.45 L/L |
| Mean cell volume | 77.1 fL | 80–99 fL |
| Mean cell haemoglobin | 21.4 pg | 26.0–33.5 pg |
| Mean cell haemoglobin concentration | 276 g/L | 300–350 g/L |
| Red cell distribution width | 17.1% | 11.5–15.0% |
| Mean platelet volume | 8.3 fL | 7–13 fL |
| Neutrophils | 4.57 × $10^9$/L | 2.0–7.5 × $10^9$/L |
| Lymphocytes | 1.47 × $10^9$/L | 1.2–3.65 × $10^9$/L |
| Monocytes | 0.36 × $10^9$/L | 0.2–1.0 × $10^9$/L |
| Eosinophils | 0.01 × $10^9$/L | 0.0–0.4 × $10^9$/L |
| Basophils | 0.02 × $10^9$/L | 0.0–0.1 × $10^9$/L |
| Ferritin | 20 µg/L | 30–150 µg/L |
| Serum iron | 8 µg/L | 5–30 µg/L |
| Transferrin saturation | 8.5% | 20–55% |

A week later, Virginia returns to discuss the results of her investigations.

## Question 4

What management options would you discuss with her?

**Further information**

Virginia opts for pharmaceutical treatment, taking 1000 mg of tranexamic acid (TXA; two 500 mg tablets) three times per day during the first three days of her period. She also commences 100 mg of oral iron taken daily. A further review is planned for three months time.

After three months, Virginia returns to say that she stopped taking her oral iron tablets because of constipation and still reports symptoms of tiredness and dizziness. She even tried taking the iron tablets on alternate days. Her periods remain heavy and more prolonged than before. Just before her appointment, she attended for a pre-arranged full blood examination and ferritin test, which again showed no improvement in her haematological parameters.

## Question 5

How would you approach her problem now?

**Further information**

Virginia undergoes ultrasonography of her pelvis; the report is as follows:

Transabdominal and transvaginal ultrasound scan was performed on day 5 of the menstrual cycle. The liver, kidneys and abdominal structures were noted to be normal. The uterus is anteverted and slightly enlarged, measuring 10 × 6 × 5 cm. The endometrial lining measured 20 mm in the anteroposterior plane with suspicion of an endometrial polyp measuring 12 mm with a feeder vessel. The myometrium appeared smooth with no evidence of adenomyosis or fibroid. Both ovaries were noted to be normal with no cyst noted. There was a small amount of free fluid in the Pouch of Douglas, consistent with the history of a recent period.

Two weeks later, you discuss the ultrasound scan report with Virginia via telehealth consultation. She is worried that she may have cancer.

## Question 6

What would your next steps be?

## CASE 3 Answers

### Answer 1

The initial assessment of a woman presenting with symptoms of HMB includes capturing a detailed medical, sexual and reproductive history, assessing the impact on quality of life, enquiring about symptoms of iron deficiency and anaemia, and excluding pregnancy.[1]

Menstrual history should be captured in detail, including duration of the problem, regularity of menstrual cycles, heaviness, timing and pattern of bleeding. Postcoital bleeding, irregular menstrual cycles and intermenstrual bleeding are different to HMB and warrant further investigation for cervical, endometrial or anovulatory causes. It is important to establish Virginia's sexual and reproductive health along with cervical screening status.

In Virginia's case, she has completed her family, having had tubal occlusion performed, so pregnancy is unlikely but should always be considered a possibility. Exploration should include symptoms of pelvic pain or pressure in the pelvis from pelvic masses such as fibroids or ovarian masses, and fatigue from anaemia. It is important to exclude symptoms associated with polycystic ovary syndrome (PCOS); that is, a history of weight gain, acne, hirsutism and irregular bleeding. It is recommended to assess symptoms related to possible thyroid disease (eg hypothyroidism) and medication history, particularly any anticoagulation therapy.

General symptoms of fatigue, dizziness or heart palpitations may suggest iron deficiency. Any history suggesting a bleeding disorder, or a strong family history of bleeding disorders, should be captured, as von Willebrand disease may be associated with HMB.

### Answer 2

A general examination should be conducted to exclude signs of anaemia, thyroid enlargement and abdominal mass. It is recommended to assess her weight and BMI and look for signs of hirsutism. With appropriate consent, a bimanual pelvic examination to identify any palpable mass or abnormal uterine size could be conducted, unless this would be clinically inappropriate. Where appropriate, it is recommended to obtain a cervical screening test according to the National Cervical Screening recommendations.[2] Pregnancy should be excluded with a urinary β-human chorionic gonadotropin test if indicated.

HMB is common and affects one in three women of reproductive age, with over half of these women being iron deficient.[3,4] HMB is described as a loss of >80 mL of blood per cycle, translating to approximately 1 L of blood loss per year. Clinically, HMB is identified in women experiencing any of the following symptoms:[4]

- bleeding through clothes
- passing blood clots greater in size than a 50-cent coin
- using double protection, such as a tampon with a sanitary pad
- need for sanitary product changes frequently overnight.

Further assessment may be aided by using the menstrual pictogram.[5]

### Answer 3

HMB falls under the umbrella term of abnormal uterine bleeding (AUB), which describes the symptoms that interfere with a women's quality of life and can be the result of three main causes:[5]

- hormonal – including anovulatory bleeding and, more commonly, bleeding where no physical cause is evident
- uterine – causes such as endometrial polyps, fibroids or malignancy
- haematological – such as from von Willebrand disease or the use of anticoagulants.

The causes of AUB can be classified into structural and non-structural causes, as outlined by the International Federation of Gynecology and Obstetrics (FIGO) PALM-COEIN system. These structural causes include Polyps, Adenomyosis, Leiomyoma (fibroids), Malignancy or hyperplasia (PALM). Non-structural causes include Coagulopathy, Ovulatory, Endometrial, Iatrogenic or Not yet classified (COEIN).[6]

AUB includes any departure from normal menstruation or from a normal menstrual cycle pattern, such as intermenstrual bleeding and postcoital bleeding, although HMB is the most common. The most common cause (>50%) of AUB is a local disorder of the clotting mechanism of the endometrium resulting in HMB, with no obvious test available for diagnosis. In terms of structural causes, fibroids constitute 30% of AUB causes, while polyps constitute 10%.[7]

In Virginia's case, her history and examination would suggest that she has HMB with low likelihood of endometriosis or fibroid uterus. She has no history suggestive of PCOS or risk factors of endometrial cancer.

Further investigations will depend on a careful history and presentation, which might include testing for haemostatic disorders (eg von Willebrand disease), thyroid dysfunction, a cervical screening test (if clinically indicated) and ultrasonography for the assessment of uterine abnormalities.[2,7] Hormonal testing is not indicated and adds no value.[7]

## Answer 4

The blood results indicate Virginia has iron deficiency anaemia. There are two key components to treating Virginia: first to reduce future iron loss and second to replenish the iron stores. The initial treatment for her HMB is pharmaceutical, which includes:[1,8,9]

- nonsteroidal anti-inflammatory drugs, which can bring about a 25% reduction in menstrual loss
- a levonorgestrel-releasing intrauterine device, which reduces menstrual loss by 80%
- the combined oral contraceptive pill, which can also help with dysmenorrhoea – this is better suited for younger women where future fertility is desired
- TXA, an antifibrinolytic, which can result in up to a 40% reduction in menstrual loss.

The use of TXA is a simple intervention for HMB. Bleeding activates the process for fibrin strand construction to clot the blood and consequently reduce blood loss. In response, tissue plasminogen activator (TPA) binds to lysine receptors on the protease plasminogen to convert to plasmin, which degrades fibrin and dissolves the clot. TXA is an amino acid that blocks the lysine plasminogen receptor and prevents TPA binding, therefore promoting clot stabilisation and reducing blood loss.[1,9] Further details of the approach to the treatment regimen can be found in the *Therapeutic guidelines*.[10]

The result of HMB can be a slow but insidious iron deficit every month, and for Virginia this has led to the development of iron deficiency anaemia. The options of oral versus parenteral iron therapy should be discussed. Iron infusion would be indicated for iron deficiency treatment where oral iron has been refractory or is not well tolerated.[11,12]

## Answer 5

Virginia was not able to tolerate her oral iron therapy, and after appropriate advice has been provided to mitigate these adverse effects (eg alternate-day dosing or reduced doses), and because she remains symptomatic from her iron deficiency anaemia, parenteral iron infusion is indicated. An iron infusion should be arranged for Virginia.

Furthermore, as there has been no improvement in her HMB after initial pharmaceutical treatment, further investigation is warranted. Ultrasonography of her pelvis should be arranged.

## Answer 6

Ultrasonography performed on day 5–10 of the menstrual cycle allows the most accurate measurement of endometrial thickness, which is used in risk assessment for endometrial hyperplasia and malignancy and improves detection of polyps.[13,14] As the ultrasound scan has shown a suspected endometrial polyp, referral for specialist evaluation is indicated. Virginia's current symptoms suggest the next stage will be hysteroscopy, dilatation and curettage, and endometrial polypectomy. The option of inserting the levonorgestrel intrauterine system (LNG-IUS) should also be provided. Virginia could be reassured that she has no risk factors of cancer as she is <45 years of age, has no abnormal bleeding such as intermenstrual bleeding, has a BMI in the healthy range and has no predisposing history such as PCOS or diabetes.[13]

Endometrial polyps may be benign or malignant; in a woman with no prior risk factors, the majority are benign. Removal of the polyp may help to resolve the symptoms, but if HMB persists, treatment with progestogens offers the best chance of resolution. This can be in the form of oral therapy, such as cyclical norethisterone, or injectable progestogens.[15] However, oral preparations are dependent on patient compliance, and injectables are non-reversible in the short term.

Hormone-containing intrauterine devices such as the LNG-IUS release progestogens locally and result in thinning of the endometrium and suppression of ovulation. It is important to advise women that they could expect irregularity of their menstrual cycles initially and to wait for at least six cycles for a noticeable improvement in their symptoms.[16] Functional ovarian cysts are commonly seen in women using the LNG-IUS, with an incidence that varies between 5% and 30%, but for the majority of women the enlarged follicles are asymptomatic, being diagnosed on routine ultrasonography, and resolve spontaneously within the first few months following diagnosis.[14] This LNG-IUS approach results in resolution of HMB in 80–90% of women by achieving oligomenorrhoea or amenorrhoea.[16] When this approach is not successful, surgical options can be considered and offered.

A woman who has AUB from benign causes and who is considering surgical management is offered a uterine-preserving procedure, if clinically appropriate. When surgical options are being considered, the least invasive procedure should be prioritised appropriate to the woman's clinical situation, including endometrial ablation and/or removal of any local pathology (eg fibroids and polyps). Where appropriate, other approaches include hysteroscopic resection, myomectomy or fibroid-necrosing procedures (eg uterine artery embolisation).[17]

Hysterectomy is considered after uterine-preserving procedures have been unsuccessful. This procedure can be performed laparoscopically, by laparotomy or vaginally, depending on the clinical situation. As this is a major procedure, the risks discussed should include: the irreversible nature of the surgery; consequences for childbearing; risk of infection, organ damage and blood loss; as well as the time in hospital and recovery period.[18]

## Conclusion

In the clinical setting, HMB is defined as 'excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life, and which occur alone or in combination with other symptoms'.[19,20] HMB is the most common presentation of abnormal uterine bleeding in premenopausal women in both general practice and in the hospital setting, affecting 25–30% of women of reproductive age.[1] With continued HMB, there is a high risk of developing iron deficiency anaemia. Early screening is recommended to improve management and quality of life.

## Resources for doctors

- Australian Government Department of Health and Aged Care – National Cervical Screening Program, www.health.gov.au/initiatives-and-programs/national-cervical-screening-program
- The Royal Australian and New Zealand College of Radiologists – Abnormal vaginal bleeding in pre-, peri- and post-menopausal women, www.canceraustralia.gov.au/sites/default/files/publications/abnormal-vaginal-bleeding-pre-peri-and-post-menopausal-women-diagnostic-guide-general-practitioners/pdf/ncgc_a3_menopause_chart_june_2012_final.pdf

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CASE

# 4 Olivia feels exhausted during her pregnancy

Olivia, aged 27 years, is a mother who presents to you with complaints of worsening tiredness, shortness of breath and feeling generally exhausted. She is currently 29 weeks pregnant with her third child; her older children are two and seven years of age. Olivia's previous pregnancies were uncomplicated. She has just moved to the area and is seeking shared antenatal care.

## Question 1

What further history would you seek from Olivia?

### Further information

Olivia has had no other medical problems and has an unremarkable family history. During her previous pregnancy she was noted to be anaemic and took over-the-counter iron tablets. Because of her move, she has not been able to attend her most recent scheduled antenatal visit at 28 weeks but as a precaution has been taking a herbal iron supplement from the chemist.

You suspect Olivia may have iron deficiency.

## Question 2

Which examinations would you perform and investigations would you order?

### Further information

Olivia's blood test results are shown in Table 1.

**Table 1. Olivia's blood test results**

| | Result | Reference range |
|---|---|---|
| Haemoglobin concentration | 98 g/L | 115–135 g/L |
| White cell count | 12.24 × $10^9$/L | 3.0–10.0 × $10^9$/L |
| Platelet count | 224 × $10^9$/L | 150–400 × $10^9$/L |
| Red cell count | 3.42 × $10^{12}$/L | 3.95–5.15 × $10^{12}$/L |
| Haematocrit | 0.306 L/L | 0.33–0.45 L/L |
| Mean cell volume | 79 fL | 80–99 fL |
| Mean cell haemoglobin | 29 pg | 26.0–33.5 pg |
| Mean cell haemoglobin concentration | 311 g/L | 300–350 g/L |
| Red cell distribution width | 15.7% | 11.5–15.0% |
| Mean platelet volume | 8.2 fL | 7–13 fL |
| Neutrophils | 7.7 × $10^9$/L | 2.0–7.5 × $10^9$/L |
| Lymphocytes | 2.1 × $10^9$/L | 1.2–3.65 × $10^9$/L |
| Monocytes | 0.7 × $10^9$/L | 0.2–1.0 × $10^9$/L |
| Eosinophils | 0 | 0.0–0.4 × $10^9$/L |
| Basophils | 0 | 0.0–0.1 × $10^9$/L |
| Ferritin | 16 µg/L | 13–150 µg/L |
| Serum iron | 9 µmol/L | 8–30 µmol/L |
| Transferrin saturation | 10% | 20–55% |

## Question 3

What is your working diagnosis, and how would you manage Olivia?

**Further information**

You decide to prescribe a dose of 325 mg ferrous sulfate tablets to be taken once per day, with a review of the blood examination in four weeks' time.[1]

At her review, Olivia reports that she has been taking the tablets as prescribed; however, she has needed to take laxatives for constipation. Her haemoglobin concentration has increased to 105 g/L, her ferritin is 27 µg/L, transferrin saturation is 13% and C-reactive protein (CRP) is within reference ranges. Olivia reports feeling better and seems to be tolerating the iron tablets well.

## Question 4

To conclude Olivia's four-week oral iron therapy review, what would you advise?

**Further information**

Olivia continues to feel well, and she does not present to you again before labour. At a gestational age of 39+5 she is admitted to hospital after spontaneous onset of labour. Her labour is complicated by fetal distress; she undergoes an unsuccessful trial of forceps, followed by an emergency caesarean section. The baby is born in good health with an Apgar score of 9/9. The surgery is complicated by a postpartum haemorrhage, with Olivia experiencing an estimated blood loss of 1700 mL.

On admission, Olivia's haemoglobin concentration was 115 g/L. Postpartum, her haemoglobin concentration drops to 69 g/L, and the obstetric team discusses a blood transfusion. They decide against this and instead prescribe an iron infusion (ferric carboxymaltose 500 mg) prior to discharge. Olivia is instructed to visit her general practitioner at two and six weeks postpartum.

## Question 5

What is your plan for Olivia's follow-up?

# CASE 4 Answers

## Answer 1

It is important to explore the symptoms in more detail. Specific questions should ask about associated symptoms, including restless legs or muscle cramps. The timing of symptom onset and precipitating factors should be investigated to exclude venous thromboembolism, which can present either acutely (sudden onset shortness of breath and pleuritic chest pain) or can be more insidious in onset over several weeks. Clinical history should be reported, including any history of gestational diabetes, family history of diabetes, history of hypothyroidism, iron deficiency and anaemia.[2]

## Answer 2

Routine observations should be carried out, including pulse, blood pressure, consideration of COVID-19 testing and pulse oximetry. Urine testing should be carried out to exclude urinary tract infection and diabetes. Blood testing should be ordered, including a full blood examination, iron studies (ferritin and transferrin saturation), vitamin B12, folate and CRP.

## Answer 3

Your working diagnosis for Olivia is iron deficiency anaemia (IDA). In pregnancy, IDA is diagnosed where ferritin is <30 µg/L and haemoglobin is <110 g/L in the first and third trimester or <105 g/L in the second trimester.[2] Of note, the mean cell volume is a late change to indicate iron deficiency, and comparison to previous results may show a trend downwards.

## Answer 4

Olivia should continue taking the iron sulphate tablets daily as she is tolerating these well and feeling better, and her haemoglobin concentration has improved. There are

no signs of inflammation, and the results of her iron studies have improved. There is no reason to increase the dose or suggest an iron infusion at this time, but she should be encouraged to continue the oral iron therapy. As she is getting mild side effects of constipation, tolerance could be improved by altering iron therapy dosing to alternating days. As Olivia remains compliant to the oral iron preparation, you can expect her to improve further until delivery. Further monitoring is required, as half of the maternal iron needed for fetal development is delivered in the last month of pregnancy.

Table 2 outlines the potential fluctuations of iron throughout a year where there is pregnancy. The body contains approximately 3000–4000 mg of iron, with approximately 1–2 mg of iron lost daily; the majority is lost through the skin from sweating or shedding. The gestation of pregnancy alone depletes the body of approximately 1200 mg of iron, while labour costs approximately 250 mg through blood loss, where there is no haemorrhage. If the mother chooses to breastfeed, this can cost the maternal body a further 200 mg of iron.[3]

**Table 2. Iron demand during pregnancy**

| Route of iron loss/gain | Iron (mg) |
|---|---|
| Skin | –1000 |
| Dietary absorption | 1500 |
| Gestation | –1200 |
| Typical labour | –250 |
| Breastfeeding | –200 |
| **Net iron** | **–1150** |

## Answer 5

You should be guided by Olivia's clinical presentation. In the setting of blood loss and IDA, she will likely recover her haemoglobin concentration within 3–4 weeks after her iron infusion. Postpartum recovery can be complicated by many factors; therefore, you should monitor her for signs of postnatal depression; check her physical, psychosocial and emotional health; and review the wellbeing of her baby.[4] Olivia's blood examination should be repeated at six weeks, including a full blood examination, iron studies and CRP. With previously marginal iron stores and a history of iron deficiency, the majority of the iron from the infusion would have contributed to erythropoiesis. Olivia received a conservative, most likely inadequate dose of intravenous iron; blood loss of 1700 mL is the equivalent of 750–900 mg of iron (approximately 0.5 mg of iron per mL of blood), so although there will be an improvement in her blood examination results, she may require further iron replacement to replenish her storage iron.[5]

Dose calculation can be undertaken with the Ganzoni equation:

Total iron deficit = weight (kg) × (target haemoglobin – actual haemoglobin in g/L) × 2.4 + iron stores (mg).

Due to the impracticalities of dose calculation from the Ganzoni formula, many clinicians apply product-specific protocols for intravenous iron dosing, or a simplified formula of 20 mg of iron per kilogram of the patient's body weight up to a maximum dose of 1000 mg.[5]

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CASE

# 5 Gustav has fatigue and increased bowel frequency

Gustav, aged 30 years, presents with a background of ulcerative colitis, for which he takes mesalazine tablets. He presents to you with increasing fatigue and increased bowel frequency with occasional episodes of blood in the stool over the past few months. He looks notably pale and unwell.

## Question 1

What history would you seek from Gustav?

## Question 2

What would you assess on examination?

### Further information

Gustav reports that his bowel frequency has increased from one to four times per day; he describes his stools as loose and bloody. He has a sense of urgency to open his bowels (tenesmus) and finds himself opening his bowels once throughout the night. These symptoms have only begun in the past two months, with worsening fatigue over the past month. He has a typically omnivorous diet and does not have any abdominal pain, fevers, arthralgia, skin changes, bleeding symptoms or weight changes. He does not recall any sick contacts or infective triggers for colitis. He is adherent to ulcerative colitis medications and takes no additional medications. His mood has been good, and he does not report any lifestyle or psychosocial triggers contributing to the symptoms.

On examination, Gustav is pale and has a heart rate of 90 beats/min and blood pressure of 120/60 mmHg. Gustav has pale conjunctivas and looks fatigued but is afebrile. Heart sounds are dual, and there is lower abdominal quadrant tenderness without palpable masses or guarding. There are no signs of extracolonic features related to ulcerative colitis and no palpable lymphadenopathy.

## Question 3

What is the likely diagnosis, given Gustav's history and examination findings?

## Question 4

Which diagnostic investigations should be considered to determine the cause of Gustav's symptoms?

### Further information

Gustav undergoes full blood examination; urea, electrolyte and creatinine; iron studies, C-reactive protein; erythrocyte sedimentation rate; faecal calprotectin and faecal polymerase chain reaction pathology testing. His results are shown in Table 1.

**Table 1. Gustav's test results**

| | Result | Reference range |
|---|---|---|
| Haemoglobin concentration | 95 g/L | 135–180 g/L |
| White cell count | 13 × $10^9$/L | 4.00–11.00 × $10^9$/L |
| Platelet count | 361 × $10^9$/L | 150–400 × $10^9$/L |
| Red cell count | 4.51 × $10^{12}$/L | 4.5–6.5 × $10^{12}$/L |
| Haematocrit | 0.26 L/L | 0.4–0.54 L/L |
| Mean cell volume | 77 fL | 80–100 fL |
| Red cell distribution width | 16% | 9.0–15.0% |
| Ferritin | 90 µg/L | 30–620 µg/L |
| Serum iron | 10 µmol/L | 9–30 µmol/L |
| Transferrin saturation | 7% | 10–45% |
| C-reactive protein | 35 mg/L | <5 mg/L |
| Erythrocyte sedimentation rate | 40 mm/hr | <14 mm/hr |
| Faecal calprotectin | 214 µg/g | <100 µg/g |
| Faecal polymerase chain reaction | Negative | |
| Blood film | Microcytic normochromic red blood cells | |

Gustav is likely experiencing a moderate flare of his ulcerative colitis as per severity markers based on his Truelove and Witts Severity Index for Ulcerative Colitis,[1] as he would score points for his four bowel movements per day, blood in stool, heart rate of 90 beats/min, anaemia and elevated erythrocyte sedimentation rate (ESR). Gustav is subsequently seen by his gastroenterologist, who escalates his treatment for his moderate ulcerative colitis flare. The gastroenterologist has kindly asked if you could assist in managing Gustav's anaemia.

## Question 5

How would you interpret Gustav's blood results for the cause of his anaemia?

## Question 6

How would you manage Gustav's anaemia?

# CASE 5 Answers

## Answer 1

Initial history should focus on:

- bowel movements – normal bowel movements; current number per day; nature of stool; amount of blood in stool; presence of tenesmus, abdominal pain and extracolonic symptoms (oral ulcers, rash, arthralgia, eye symptoms) and nocturnal symptoms; possible infective triggers should be sought
- possible anaemia causes – adequacy of dietary iron, whether he has been supplementing with oral iron (which may cause increased bowel frequency), potential bleeding
- red flag symptoms – significant weight loss, lymphadenopathy, new lumps/lesions, night sweats, and particularly considering the association of ulcerative colitis with colorectal cancer
- details of last colonoscopy.

Establishing timelines for both fatigue and bowel habits would be important to accurately characterise Gustav's profile. Establishing adherence to ulcerative colitis medications may prompt a reason for Gustav's symptoms. Given the presentation of fatigue, it would be recommended to consider other potential biopsychosocial factors, such as:

- lifestyle – drug, alcohol, history, sleep hygiene, physical activity, occupation and associated stressors
- biological – coeliac disease, endocrine conditions, sleep apnoea, recent infections (including viral)
- psychosocial – mood disorder, stress, anxiety.

## Answer 2

Important elements of the examination include general appearance (pallor, rash); vital signs such as presence of tachycardia, hypotension, fever, hypoxia and tachypnoea; and hydration status. Systemic specific examination should include:

- gastroenterology – abdominal tenderness; lymph nodes; extraintestinal ulcerative colitis symptoms including rash, eye involvement, inflammatory arthritis
- cardiovascular – tachycardia, hypotension, postural blood pressure drop, fluid status, heart sounds, cyanosis.

## Answer 3

Gustav likely has colitis, and given his background, the most likely diagnosis is a flare of ulcerative colitis, which is resulting in increased bowel frequency, abdominal pain and bloody stool. Colitis infections, such as viral and bacterial causes, should also be considered. Common infective agents may include bacteria such as *Shigella* spp., *Escherichia coli, Campylobacter* spp., *Salmonella* spp., *Yersinia* spp. and *Clostridium* spp. Parasitic causes include *Entamoeba* spp. and *Schistosoma* spp., and viral causes such as Cytomegalovirus should be considered as well, although these are less likely. *Campylobacter* spp. and *Shigella* spp. are most likely to cause bloody bowel movements. The fatigue is likely driven by the iron deficiency and associated anaemia. This may be absolute due to blood loss or secondary because of inflammation relating to his presumed flare of ulcerative colitis, causing functional iron deficiency.

## Answer 4

Relevant investigations should focus on confirming the working diagnosis and excluding relevant differential diagnoses.

### Blood investigations

- Full blood examination and blood film with haemoglobin (Hb) concentration measurement to confirm anaemia (Hb <120 g/L in women and <130 g/L in men). The mean cell volume, red cell distribution width and blood film should all be reviewed as they may suggest iron deficiency or alternative aetiology.
- Relevant biochemistry including urea, electrolytes and creatinine to screen for prerenal or renal dysfunction from hypovolaemia.
- Liver function test – serum albumin may be low, which may suggest active inflammation and is commonly used as a disease severity marker in ulcerative colitis. Liver function tests may also indicate a possible liver aetiology of fatigue such as primary sclerosing cholangitis, which is seen in higher rates in patients with ulcerative colitis. Expectant derangement would be in bilirubin, alkaline phosphate and gamma glutamyl transferase, which may be elevated.
- Inflammatory markers – C-reactive protein (CRP) and ESR suggest the presence and severity of inflammation.
- Iron studies including ferritin level, transferrin level, transferrin saturation. Additional testing of soluble transferrin receptor, if available, may be useful to determine the aetiology of anaemia as it is increased in iron deficiency anaemia.

### Microbiology

- Faeces microscopy, culture and sensitivity; enteric polymerase chain reaction – to exclude infective causes of gastrointestinal symptoms.
- Faecal calprotectin – to assess for possible colonic inflammation. Faecal calprotectin is a biochemical measurement of calprotectin in the faeces, which is a calcium- and zinc-binding protein that is mainly found in neutrophils. The measurement of calprotectin in the faeces suggests neutrophil migration into the gastrointestinal tract due to inflammation and is therefore a good marker of intestinal inflammation.[2]

## Answer 5

Gustav's blood results confirm he has a normocytic anaemia and evidence of an inflammatory process as seen by his CRP, ESR and albumin level. Serum ferritin is in the normal range, but he has a decreased transferrin saturation level (<20%).

Gustav likely has both absolute and functional iron deficiency anaemia, which often coexist in patients with inflammation. Absolute iron deficiency refers to insufficient body iron stores for erythropoiesis – in this case likely due to blood loss from colonic bleeding from his ulcerative colitis. Functional iron deficiency is a complex diagnosis where inflammation results in inadequate mobilisation for erythropoiesis despite sufficient body iron stores resulting in anaemia.[3]

Functional iron deficiency (synonymous with anaemia of inflammation) is diagnosed with normal or increased ferritin with associated transferrin saturation <20% in a patient with evidence of systemic inflammation (as evident with elevated CRP).[4] Functional iron deficiency reflects complex pathways; however, key is that inflammation upregulates hepcidin, which sequesters circulatory iron into ferritin storage and reduces dietary iron absorption – globally reducing the body's access to iron. While normally in iron deficiency states the serum ferritin should be depressed, ferritin acts as a positive inflammatory marker as it is secreted by macrophages and hepatocytes in inflammatory states, which can further result in elevated plasma ferritin levels.[4]

Secondly, absolute iron deficiency can coexist with functional iron deficiency. This is typically diagnosed when the serum ferritin level is <100 μg/L, alongside serum transferrin saturation <20% and evidence of inflammation.[4] A serum ferritin level >100 μg/L makes absolute iron deficiency less likely. Absolute iron deficiency can be due to more typical iron deficiency causes including bleeding or dietary considerations.[5]

It is important to note that serum iron levels do not accurately represent body iron stores because of the

**Table 2. Trends in serum values across differing presentations of anaemia*[10]**

| | Absolute iron deficiency anaemia | Functional iron deficiency anaemia | Absolute and functional iron deficiency anaemia |
|---|---|---|---|
| Serum iron | Decreased | Decreased | Decreased |
| Transferrin | Increased | Decreased or normal | Decreased |
| Transferrin saturation | Decreased | Decreased | Decreased |
| Ferritin | Decreased (<30 µg/L) | Increased (>100 µg/L) | Variable but usually <100 µg/L |
| Soluble transferrin receptor | Increased | Normal | Increased or normal |
| C-reactive protein | Normal | Normal or increased | Increased |
| Erythropoietin | Increased | Normal or slightly increased for the degree of anaemia | Increased or normal |

**This includes absolute iron deficiency anaemia, functional iron deficiency anaemia of mixed origin.*

relatively small amount of iron in plasma (2–3 mg), compared with the total body stores of 3000–4000 mg of iron. Serum iron levels are highly variable and are unstable when iron demands change during various body states, fasting status and diurnal variations.[6]

Differentiation between absolute iron deficiency and functional iron deficiency can often be difficult because of heterogeneity in the blood testing as a result of the underlying inflammatory processes.

An emerging marker to differentiate the aetiology of anaemia is the soluble transferrin receptor test (Table 2). Plasma soluble transferrin receptor level is elevated if there is an increased iron demand, regardless of inflammation status.[7] A raised soluble transferrin receptor can help confirm the presence of at least absolute iron deficiency anaemia, noting that concurrent anaemia causes may also exist. It should be noted, however, that this test is not readily available.

## Answer 6

Given Gustav is experiencing both functional iron deficiency and absolute iron deficiency anaemia, most likely from his ulcerative colitis inflammation, he will not only require a correction of his iron deficiency but a reduction in inflammation to help protect his long-term iron status. His treatment from the gastroenterologist targeting his ulcerative colitis flare should improve his inflammation levels.

For the correction of iron deficiency, the route of iron replacement needs to be tailored to the patient's condition; in this case, intravenous iron would be preferred over oral iron supplementation. Given Gustav's inflammatory colitis state, hepcidin expression will be upregulated, resulting in reduced iron absorption by duodenal enterocytes, making it more difficult to absorb oral iron.[6] Non-absorbed oral iron can result in increased inflammation and alteration of the microbiota profile and metabolism, resulting in an increased incidence of abdominal pain, diarrhoea or nausea.[8] Of note, these side effects of oral iron can occur without an inflammatory process, resulting in discontinuation in up to 21% of patients.[9] If there is mild ulcerative colitis inflammation, then oral iron supplementation can be considered but would still not be preferred over intravenous iron treatment.[3]

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**ACTIVITY ID** **384419**

## Iron deficiency

This unit of *check* is approved for 10 hours of CPD Activity (two hours per case). The 10 hours' when completed, including the online questions, comprise five hours' Education and five hours' Reviewing Performance.

To complete this unit as a CPD Activity, you should carefully read all cases, complete the questions for each case (hard copy or online), answer the linked multiple-choice questions online and score >80%, and complete the evaluation form online.

All doctors also need to do a minimum five hours' Measuring Outcomes CPD each year, and you can do this by completing one Mini-Audit each year. You can do a Mini-Audit based on this unit, or any other unit of *check*, or on any topic that is relevant to your practice.

To do a Mini-Audit on this unit's topic, select the last five patients you managed with iron deficiency. Review their records, summarise your management and findings, and indicate in writing (for yourself) where your management and patient outcomes could have been improved, based on what you have learned following your completion of this *check* unit.

You can access all online resources here: https://mycpd.racgp.org.au

For any technical issues, including guides and templates for a Mini-Audit, contact us on 1800 284 789. To purchase this unit if you are not an RACGP member, please call 1800 284 789.

### Case 1 – Aidan

Patricia comes to see you with her son Aidan, aged 25 months, who has been diagnosed with iron deficiency anaemia.

#### Question 1

Which one of the following do you advise?

**A.** To take oral iron tablets on alternate days at a dose of 80 mg elemental iron

**B.** To introduce 200 mL of cow's milk after each main meal and incorporate iron-rich foods into the diet

**C.** To incorporate iron-rich foods into the diet and take 3 mg/kg/day liquid iron

**D.** To take 3 mg/kg/day liquid iron with 200 mL of cow's milk after each main meal

#### Question 2

Which one of the following increases a toddler's risk of iron deficiency?

**A.** Consuming >500 mL of cow's milk per day

**B.** Consuming meat

**C.** Consuming leafy greens

**D.** Consuming legumes

#### Question 3

Iron deficiency should be treated in which one of the following situations?

**A.** Only if the patient is anaemic

**B.** If there are ongoing risk factors for the development of anaemia

**C.** If the patient is symptomatic

**D.** When the patient is diagnosed

#### Question 4

Which one of the following would be the first-line treatment for iron deficiency **without** anaemia?

**A.** Dietary modifications

**B.** Oral iron

**C.** Intravenous iron

**D.** No treatment as the patient is not anaemic

### Case 2 – Gurpreet

Gurpreet, aged 32 years, presents reporting heavy bleeding during her most recent periods over the past few months.

#### Question 5

In premenopausal women, what is the most common structural cause of abnormal uterine bleeding (AUB)?

**A.** Endometrial polyps

**B.** Fibroids

**C.** Endometriosis

**D.** Polycystic ovary syndrome

**Further information**

Heavy menstrual bleeding (HMB) can be associated with insidious onset of iron deficiency or iron deficiency anaemia. If left untreated, it can cause symptoms of fatigue, palpitations and poor quality of life.

### Question 6

Which one of the following is another health impact that chronic iron deficiency or iron deficiency anaemia can have on a woman with HMB?

**A.** Renal failure

**B.** Frequent urination

**C.** Increased risks of blood transfusion from surgery

**D.** Chronic pelvic pain

## Case 3 – Nuala

Nuala, aged 28 years, is 20 weeks pregnant and presents reporting increasing tiredness and fatigue. You suspect she may be experiencing iron deficiency.

### Question 7

Assuming no suspicion of venous thromboembolism and previous testing for hypothyroidism and diabetes, which one of the following combinations of tests are required?

**A.** Full blood examination, ferritin, transferrin saturation, vitamin B12, folate, C-reactive protein

**B.** Full blood examination, iron, vitamin B12, folate, D-dimer, transferrin saturation

**C.** Full blood examination, vitamin D, vitamin B12, C-reactive protein

**D.** Ferritin, vitamin B12, folate, transferrin saturation

#### Further information

Nuala continues to experience difficulty in maintaining her iron level and presents during the last month of pregnancy with severe iron deficiency anaemia. Her haemoglobin concentration of is 80 g/L and ferritin is 6 µg/L.

### Question 8

Which one of the following treatments would be best recommended?

**A.** An iron infusion at a dose of 20 mg/kg

**B.** Oral iron supplementation taken at a dose of 300 mg daily

**C.** Increased dietary iron and more inclusion of leafy greens and meat products

**D.** Oral iron supplementation taken at a dose of 65 mg on alternate days

## Case 5

Tiegan, aged 40 years, has a background of Crohn's disease and presents with increasing bowel movements and pallor. You suspect anaemia as well as increased inflammation from her Crohn's disease.

### Question 9

Which marker of iron deficiency is the least reliable?

**A.** Ferritin

**B.** Serum iron

**C.** Haemoglobin concentration

**D.** Transferrin saturation

### Question 10

A serum ferritin level greater than which one of the following levels would likely exclude absolute iron deficiency contributing to Tiegan's anaemia in this case?

**A.** 10 µg/L

**B.** 50 µg/L

**C.** 70 µg/L

**D.** 300 µg/L


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