

education

FROM THE JOURNALS Edited highlights of weekly research reviews

Buckling under pressure

Children break their wrists with alarming ease and frequency. The commonest type of fracture in children is a torus (from the Latin for protuberance) or buckle fracture, in which the soft, compressible radius and ulna bend or crack under the impact of a fall but don't break into the cortex.

Approaches to treatment differ, and this large multicentre UK trial found that treatment with a bandage and immediate discharge was as safe and effective as rigid immobilisation (using a wrist splint in 97% of cases and plaster cast in 3%) and routine follow-up regardless of the age of the child. No one needed surgery or fracture manipulation. The bandage group used more analgesia in the first 24 hours, but, overall, the rate of complications, pain, return to school, and self-reported function scores didn't differ between the two groups at six weeks after the injury.

• *Lancet* doi:10.1016/S0140-6736(22)01015-7

Polypill: no panacea

A polypill for cardiovascular protection was first proposed more than 20 years ago but still isn't widely available. Critics say you lose flexibility in prescribing, whereas advocates say one pill is easier to swallow than a handful. This multicentre European trial of 2499 people who had survived a heart attack within the previous six months found that a daily polypill (100 mg aspirin; 2.5, 5, or 10 mg ramipril; and 20 or 40 mg atorvastatin) resulted in a significantly lower risk of further major cardiovascular events than usual care (8.2% v 11.7%) over a two year period. The vast majority of people in the usual care group were prescribed the same three drugs, but adherence differed significantly (74.1 v 63.2% at 2 years).

Disappointingly, the polypill didn't reduce the number of deaths from all causes; in fact, more people died of cancer in the polypill group; presumably because, if you're protected from dying of a heart attack or stroke, you live long enough to develop cancer. The mean age of participants was 76 years, and over half were current or former smokers.

• *N Engl J Med* doi:10.1056/NEJMoa2208275

The heart and HIV

The life expectancy of people living with HIV infection in high income countries has improved, though it is still around nine years less than HIV negative people. Greater longevity is associated with a rising prevalence of HIV associated cardiovascular disease. This systematic

review of 45 studies including 5218 people living with HIV and 2414 without, with a mean age of 49 years, found that advanced cardiovascular imaging identified signs of moderate to severe coronary disease in 0-52% of those with HIV and 0-27% of those without, and signs of myocardial fibrosis in 5-84% versus 0-68%. It's hard to know what to make of these results given the large degree of heterogeneity, the confounding effect of risk factors not associated with HIV, and the lack of data from low income countries with higher rates of endemic HIV infection.

• *JAMA* doi:10.1001/jama.2022.15078

Steps in the right direction

This population based, prospective cohort study using UK Biobank data for 78 500 individuals (mean age 61) found that more steps per day (up to about 10 000 steps) measured on a wrist accelerometer were associated with a lower risk of all cause cancer and cardiovascular disease mortality and cancer and cardiovascular disease incidence over a seven year follow-up period. The fact that the benefit fell off over 10 000 steps was probably because of small sample size rather than anything magical about the 10 000 figure. It is fair to assume that the more steps, the better. The main problem with this study is the usual one for cohort studies; you really can't claim that walking causes the lower risk. But encouragingly walking is a public health no-brainer: low risk, cheap, and, at the very least, associated with good mental and physical wellbeing.

• *JAMA Intern Med* doi:10.1001/jamainternmed.2022.4000

Incidentally

What do you do about adrenal incidentalomas (AIs)—the asymptomatic adrenal tumours that show up in up to 5% of abdominal CT scans and whose incidence rises with age? This cross sectional study in China found that 1.4% of 25 356 people who attended a routine annual check that included adrenal CT were found to have an adrenal tumour. There were no cases of malignancy or pheochromocytoma, and most of the tumours were adrenocortical adenomas. Only 63% of those with adenomas had endocrine testing, but, of those who did, most had normal cortisol levels (72% irrespective of age). In the UK, imaging, endocrine screening, and management by a multidisciplinary team are recommended when AIs over 1 cm in diameter are identified. But patients can, meanwhile, be reassured the chances are that their AI will prove to be purely incidental and harmless.

• *Ann Intern Med* doi:10.7326/M22-1619

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Covid-19 vaccination in pregnancy

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0.5 HOURS

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This is a summary of a State of the Art Review *Covid-19 vaccination in pregnancy*, published recently on [bmj.com](https://www.bmj.com). The full article is available at <https://www.bmj.com/content/378/bmj-2021-069741>

Several million cases of covid-19 during pregnancy are expected to have occurred in the past two years, making SARS-CoV-2 infection one of the most prevalent illnesses to affect this population. Pregnant women with symptomatic covid-19 infection are at increased risk for severe disease, with increased rates of hospital admission, intensive care unit (ICU) admission, intubation, and death.^{5,6,7}

Given that pregnancy was an exclusion criterion in early clinical trials of vaccines for covid-19, obstetric patients and their providers initially were required to make decisions about vaccination with limited data. Observational data have since been rapidly accumulated, and thus far confirm that the benefits of vaccination outweigh the potential risks. This review examines the evidence supporting the effectiveness, immunogenicity, placental transfer, side effects, and perinatal outcomes of maternal covid-19 vaccination.

One hundred and six countries recommend covid-19 vaccination for some or all pregnant or lactating women, whereas 15 countries specifically recommend against it

Incidence/prevalence

Pregnancy is an independent risk factor for severe covid-19.⁵ Although the absolute risk for severe maternal morbidity and mortality is low, pregnancy remains a risk factor for hospital admission, ICU admission, and need for extracorporeal membrane oxygenation related to covid-19 compared with non-pregnant women.⁵

Covid-19 in pregnancy has also been associated with an increased risk of stillbirth and maternal death,^{7,10,11} and comorbidities such as advanced maternal age, obesity, diabetes, and heart disease further increase these risks. Moreover, several cases of intrauterine transmission of SARS-CoV-2 have been documented, although the risk seems to be low.¹²

Additionally, neonates have been shown to be susceptible to severe illness from SARS-CoV-2 infection.¹³ Neonates rely on the active placental transfer of maternal IgG for their protection against pathogens during the first six months of life,^{14,15} so vaccination during pregnancy has the potential to protect both mother and neonate.

One hundred and six countries recommend covid-19 vaccination for some or all pregnant or lactating women, whereas 15 countries specifically recommend against it. Given the diversity of recommendations worldwide, the prevalence of women vaccinated for covid-19 during pregnancy likely also varies.

In the US, all major professional health organisations, including the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM), have consistently recommended that everyone who is pregnant should be vaccinated against covid-19 since early 2021^{20,21}; however, as of April 2022, the US Vaccine Safety Datalink estimated that only 69.4% of pregnant women aged 18-49 years had been fully vaccinated before or during pregnancy.²²



Covid-19 vaccines

We identified four vaccines as having published data on their use in pregnancy: Pfizer-BioNTech, Moderna, Johnson and Johnson-Janssen, and Oxford-AstraZeneca (table 1, *bmj.com*). The Pfizer-BioNTech and Moderna mRNA vaccines had the most data in pregnancy. Thus far, mRNA vaccines have shown better efficacy in the non-pregnant population than the viral vector vaccines for preventing symptomatic illness—with Pfizer and Moderna vaccines showing 95.0% and 94.1% efficacy, respectively, in the initial clinical trials—as well as severe disease, two weeks after the two dose series.^{23 25} By contrast, the Johnson and Johnson-Janssen vaccine was 72% effective in preventing symptomatic infection and 85% effective in preventing severe disease in the non-pregnant population,²⁷ and the AstraZeneca vaccine was 70.4% effective after two doses.²⁹ However, some of these differences between vaccines might be due to the variants circulating at the time of the trials.

As pregnancy was an exclusion criterion for these studies, which vaccine is the most effective in the pregnant population is unclear. No recommendation for specific timing of vaccination in pregnancy exists, and most countries recommend vaccination regardless of pregnancy trimester. Pregnancy need not be delayed after covid-19 vaccination, as none of the currently available vaccines is a live vaccine.

Covid-19 vaccine immunogenicity data in pregnancy

Available data on the humoral and functional immune response to covid-19 vaccines in pregnancy are observational. Our review identified 20 studies evaluating the immunogenicity of covid-19 vaccines in pregnancy (table 2, *bmj.com*),^{35-40 41-54} most evaluating immunogenicity of the Pfizer-BioNTech vaccine. Multiple studies support a robust maternal antibody response to covid-19 vaccination.^{40 42-45 51 54} A cohort study documented humoral immunity in pregnancy, with immunogenicity and reactogenicity similar to those observed in non-pregnant women; vaccine induced antibody titres were equivalent in pregnant and non-pregnant women.⁴² A few studies have found reduced immunogenicity in pregnancy compared with that observed in non-pregnant vaccinated women.^{38 35}

Two studies evaluated the maternal immunogenicity after a third trimester booster vaccination,^{49 54} and highlight the importance of adherence to full vaccination recommendations in pregnancy and additionally support the benefit of a booster dose in pregnancy to optimise immunity.

The degree of maternal protection via placental transfer of antibodies likely depends on maternal antibody concentration, which is related to timing of vaccination and delivery. In one study, early third trimester (27-31 weeks) vaccination was associated with higher neonatal anti-SARS-CoV-2 antibody and serum neutralising activity. This may support early third trimester as the optimal timing for a booster vaccination to optimise maternal to fetal antibody transfer for neonatal protection.⁴⁹ In general, transplacental antibody transfer starts in the second trimester; however, transfer is most efficient in the third trimester.^{55 56}

Covid-19 vaccines in prevention of maternal and infant infection

We identified nine articles evaluating risk of maternal SARS-CoV-2 infection after maternal vaccination.^{9 57-64} The data overwhelmingly support maternal vaccination as being effective at reducing the risk for infection and severe illness,^{63 60} and reflect effectiveness mainly against the original SARS-CoV-2 reference strain and the B.1.1.7 (α) variant. A retrospective cohort study in the US of 1332 vaccinated pregnant

The overall rates of adverse perinatal outcomes were not increased after maternal vaccination

patients and 8760 incompletely vaccinated or unvaccinated pregnant patients found that vaccinated patients had lower odds of severe covid-19, defined as SpO₂ <94% on room air, PaO₂/FiO₂ ratio <300 mm Hg, respiratory rate >30 breaths per minute, or lung infiltrates >50%, or critical covid-19, defined as respiratory failure, septic shock, or multiple organ failure (0.08% v 0.66%; adjusted odds ratio 0.10, 95% confidence interval 0.01 to 0.49), and covid-19 of any severity (1.1% v 3.3%; 0.31, 0.17 to 0.51).⁶²

Additionally, a study⁶⁵ of 176 infants admitted to hospital with covid-19 found that 16% of their mothers had been vaccinated compared with 32% of 203 infants admitted without covid-19 ($P < 0.01$). Effectiveness of maternal vaccination during pregnancy against covid-19 related hospital admission in infants aged <6 months was found to be 61% (31% to 78%). Effectiveness of a two dose covid-19 vaccination series was 32% (-43% to 68%) in the first 20 weeks of pregnancy and 80% (55% to 91%) after 21 weeks through 14 days before delivery. This gestational age breakdown has wide confidence intervals and should be interpreted with caution. Overall, completion of a two dose mRNA covid-19 vaccination series during pregnancy seems to reduce covid-19 related hospital admissions among infants aged <6 months, but the duration of clinical protection remains uncertain.

Covid-19 vaccines and perinatal outcomes

On the basis of 26 studies, the overall rates of adverse perinatal outcomes were not increased after maternal vaccination (table 3, *bmj.com*). The rates of preterm birth, fetal growth restriction, caesarean delivery, and neonatal intensive care unit (NICU) admission varied across studies, which is likely explained by different patient populations; however, in the studies with a comparison group of unvaccinated pregnant patients, the rates were not significantly increased.

A large registry based study of births in Sweden and Norway (28 506 vaccinated; 129 015 unvaccinated) found no significant increased risk of adverse pregnancy outcomes including preterm birth, stillbirth, small for gestational age, or NICU admission in the vaccinated group.⁷⁴ The results were similar for vaccinations during the second or third trimester, with one or two doses of vaccine, and with different mRNA vaccine types.

We identified four studies on risk of miscarriage after covid-19 vaccinations in pregnancy.⁶⁷⁻⁷⁰ One used the Vaccine Safety Datalink to analyse the odds of receiving a covid-19 vaccine in the 28 days before a spontaneous abortion.⁶⁷ It found that pregnancies ending in a spontaneous abortion did not have an increased odds of exposure to a covid-19 vaccination in the previous 28 days compared with ongoing pregnancies (adjusted odds ratio 1.02, 0.96 to 1.08). Results were consistent for Moderna and Pfizer vaccines and by gestational age group.

Six studies evaluated the risk of fetal anomalies after maternal vaccination (table 3, *bmj.com*).^{57 58 61 70 71 77} A large Israeli study of 16 738 infants prenatally exposed to the Pfizer vaccine compared with 7452 unexposed infants did a subgroup analysis among newborns exposed to first trimester vaccination (n=2021) versus unexposed newborns (n=3580) and found no difference in congenital anomalies (risk ratio 0.69, 95% confidence interval 0.44 to 1.04).⁶¹ Additionally,

the risk for major heart malformations was lower among the exposed group (risk ratio 0.46, 0.24 to 0.82). Given the importance of timing in pregnancy and risk of fetal anomalies, a large cohort study evaluating the association of covid-19 vaccination during early pregnancy with risk of congenital fetal anomalies identified an anomaly in 27 (5.1%) of 534 unvaccinated people versus 109 (4.2%) of 2622 people who received at least one dose of vaccine (P=0.35).⁷⁷ Importantly, after control for potential confounders such as haemoglobin A1c level in the first trimester and age at delivery, vaccination within the highest risk period for teratogenicity was not associated with presence of congenital anomalies identified by ultrasonography (adjusted odds ratio 1.05, 0.72 to 1.54).

We identified nine studies evaluating the risk of stillbirth after covid-19 vaccination.^{38 49 62 64 70-72 74 75} None found an increased risk; however, given the rarity of stillbirth as an event, large studies will be needed to evaluate this risk adequately.

Twelve studies evaluated the risk of preterm birth after maternal covid-19 vaccination, and the data are reassuring.^{36 38 39 42 50 61 64 70-74} One retrospective study of the Pfizer vaccine in Israel found the overall rate of preterm birth to be 5.5% in the vaccinated group compared with 6.2% in the unvaccinated group (P=0.31); however, people vaccinated in the second trimester of pregnancy (n=964) were more likely to have a preterm birth than those vaccinated in the third trimester (n=1329) (8.1% v 6.2%; P<0.001).⁷² This association persisted after adjustment for potential confounders (adjusted odds ratio 1.49, 1.11 to 2.01).

Nine studies evaluated NICU admission rates after maternal vaccination, and none identified an increased risk.^{36 38 42 50 57 64 70 74 78}

Covid-19 vaccine side effects in pregnancy

The vaccine side effect profile in pregnancy seems to be similar to that in non-pregnant people, with pain at the injection site, fatigue, headache, and myalgia being the most frequent symptoms.^{37 38 42 55 71}

Covid-19 vaccine hesitancy in pregnancy

Factors positively associated with vaccine willingness/uptake in pregnancy tend to be the same around the globe, including older maternal age, higher education, previous influenza vaccine uptake, higher level of trust in the healthcare system, increased perceived risk of covid-19, fertility treatments, urban living, and higher socioeconomic status. Factors associated with a lower likelihood of vaccination during pregnancy included younger age, lower education/socioeconomic status, and lack of adherence to influenza vaccination recommendations. Pregnancy itself was negatively associated with vaccine acceptance in several studies when a non-pregnant cohort was used for comparison.

Receipt of at least one vaccine dose was highest among Asian women (24.7%), followed by white women (19.7%), and lowest among black (6.0%) and Hispanic (11.9%) women. One study found that the impact of education and influenza vaccination history on vaccine acceptance varied depending on race, suggesting that different public health messaging might be appropriate for black or African-American women because of their lived experiences with systemic racism and mistrust in the healthcare system.⁹⁰

Another emerging theme from the data was the importance of counselling from healthcare providers. Several studies found that a provider's recommendation was positively associated with covid-19 vaccination.^{87 89 98 110}

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We provided an initial draft of the manuscript and outline of the key points of the paper to a patient who chose to be vaccinated in pregnancy and one who opted to wait until post partum. They both expressed concern about unknown fetal risks with receiving a novel vaccine in pregnancy. Both patients emphasised the importance of receiving direct vaccine counselling about their specific pregnancy from their obstetric healthcare provider.

On the basis of these observations, we modified the manuscript to ensure a focus on perinatal outcomes and vaccine hesitancy and also to acknowledge the importance of counselling by the obstetric provider.

Guidelines

WHO recommends the Johnson and Johnson-Janssen, Moderna, Novavax, Oxford-AstraZeneca, and Pfizer-BioNTech vaccines for pregnant women and permits Sinopharm, BIBP-CorV, Sinovac CoronaVac, and Bharat Biotech Covaxin. In the UK, the Royal College of Obstetricians and Gynaecologists (RCOG) prefers that pregnant women be offered the Pfizer-BioNTech or Moderna mRNA vaccines, where available, given the greater amount of data on this vaccine type and that current data have not raised any safety concerns.

In the US, the CDC, the ACOG, and the SMFM all recommend that people who are pregnant get vaccinated and stay up to date with their covid-19 vaccines, including getting a booster shot.^{20 21 121} Overall, the CDC states a preference for mRNA covid-19 vaccines over the Johnson and Johnson-Janssen vaccine for primary and booster vaccination; however, the latter vaccine may be considered in certain situations such as an allergic reaction, limited access to mRNA vaccines, or patient preference; this includes during pregnancy.

As of 12 March 2022, China's position is that covid-19 vaccination during pregnancy is not recommended, and vaccination while lactating is recommended for some or all.¹⁹ In India, the currently available covid-19 vaccines are Covishield and Covaxin.¹⁹ At present, the recommendations from the Ministry of Health and Family Welfare, Government of India, state that pregnancy and lactation are contraindications to covid-19 vaccinations.¹²² However, the Federation of Obstetric and Gynaecological Societies of India's position statement on covid-19 vaccination for pregnant and breastfeeding women states that protection from covid-19 vaccination should extend to pregnant and lactating women, given that the benefits seem to far outweigh any theoretical and remote risks of vaccination.¹²³ The International Society of Infectious Diseases in Obstetrics and Gynaecology advises policy makers and societies to prioritise pregnant women to receive vaccination against SARS-CoV-2 and favours the mRNA vaccines until further safety information becomes available.¹²⁴

Competing interests: See [bmj.com](https://www.bmj.com).

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Investigating abnormal uterine bleeding in reproductive aged women

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0.5 HOURS

A 35 year old woman presents to her GP with heavy periods, which are gradually getting worse. She is soaking through her clothes on her heaviest days and is concerned about leaving the house. She has also noticed an increased level of tiredness and inability to concentrate at work.

Abnormal uterine bleeding (AUB) is a common presentation in primary care. Estimates vary, but the prevalence among non-pregnant women of reproductive age globally is thought to be between 20% and 35%.¹⁻³ This article refers to women, but the concepts apply to all people who menstruate. AUB affects women of all ages and backgrounds, with women from ethnic minority backgrounds and those living in deprivation the least likely to seek or receive treatment.³

In the past 10 years, systems for the nomenclature and classification of AUB have been established, with the International Federation of Gynaecology and Obstetrics (FIGO) publishing guidance in 2011 and updated in 2018 to guide patient care and management of those with AUB in the reproductive years.^{2,4} The UK's National Institute for Health and Care Excellence (NICE) also published updated guidance for heavy menstrual bleeding in 2018.¹

AUB can be defined as chronic (present for more than 6 months) or acute. Acute AUB can occur on a background of chronic AUB, or occur on its own

Definitions

Abnormal uterine bleeding is the term used to encompass the symptoms of heavy menstrual bleeding and intermenstrual bleeding, and describes any bleeding from the uterus that is abnormal in flow volume, regularity, frequency, or duration.⁴ AUB is a symptom not a diagnosis. Avoid using terms such as menorrhagia, metrorrhagia, dysfunctional uterine bleeding, and oligomenorrhoea as they are ambiguous with no clear definition of what each term means.^{2,5} This ambiguity may lead to mismatches in both clinical management and translation of research into clinical practice.⁶ AUB can be defined as chronic (present for more than 6 months) or acute. Acute AUB can occur on a background of chronic AUB, or occur on its own, and is defined as "an episode of heavy bleeding ... of sufficient quantity to require immediate intervention to prevent further blood loss."⁴

Why does it matter?

Abnormal uterine bleeding is a common complaint across the globe.² Heavy menstrual bleeding alone comprises 20% of all referrals to gynaecological services in the UK,⁷ making it one of the commonest reasons that women are seen in primary and secondary care.¹ Women often normalise their symptoms,⁶ but AUB can have a negative impact on all aspects of quality of life and is related to higher rates of work absence and unemployment.⁸ AUB can negatively affect a woman's social, financial, emotional, and personal life as well as her work and relationships. AUB also has a negative impact environmentally and economically.

In a European survey, 46% of women sought no treatment or did not consult their doctor about their bleeding.⁹ A UK survey of nearly 100 000 women in 2021 found that, despite seeking help, 84% of women felt there were times their concerns were not listened to by healthcare professionals.¹⁰ Barriers to accessing care include healthcare professionals dismissing symptoms as unimportant, communication difficulties, and a lack of knowledge among women that AUB can be treated.¹¹

As part of a UK audit, women who were referred to secondary care with heavy menstrual bleeding were asked to complete a questionnaire about their experiences: up to one third of them reported receiving no treatment in primary care before being referred.³ Women from black, Asian, and minority ethnic backgrounds, and those most socially deprived, were least likely to receive treatment.³

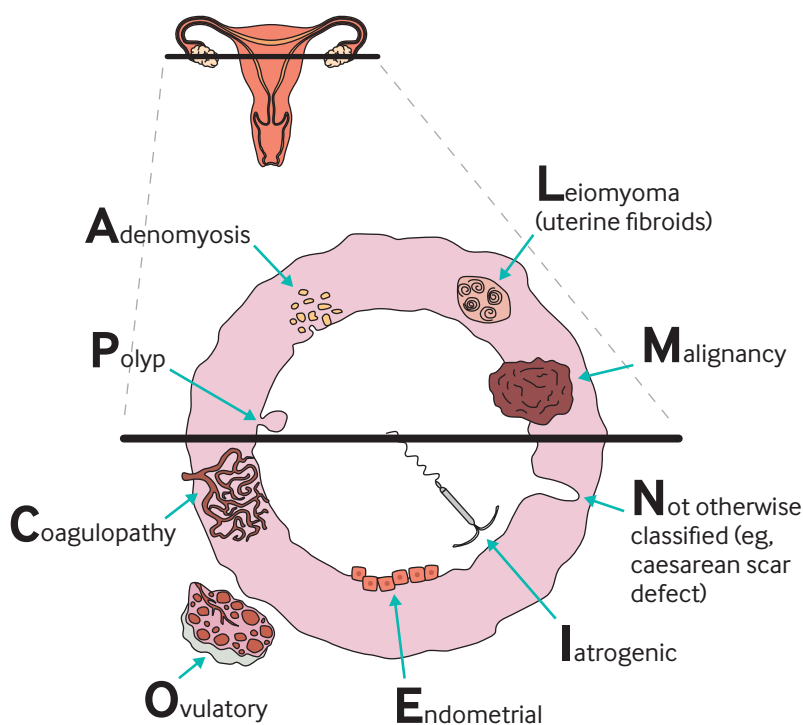
HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

A patient with a history of abnormal uterine bleeding gave her opinion on the article. She then wrote a clinical vignette describing her experience of living with heavy menstrual bleeding to complement the article.

WHAT YOU NEED TO KNOW

- Abnormal uterine bleeding (AUB) is common, and the cause must be understood in order to direct management
- AUB in the perimenopause is a risk factor for endometrial hyperplasia or malignancy, and investigation is warranted
- Iron deficiency and iron deficiency anaemia are extremely common in women with AUB and often easily remedied

Fig 1 | Schematic representation of PALM-COEIN (FIGO System 2) classification of abnormal uterine bleeding (AUB). PALM denotes the structural causes of AUB (Polyps, Adenomyosis, Leiomyoma (uterine fibroids), Malignancy and hyperplasia), and COEIN represents the non-structural causes (Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, Not otherwise classified)



Classification

The PALM-COEIN classification system, developed by FIGO in 2011,⁴ provides a standardised way of classifying the causes of AUB. It includes nine distinct causes of uterine bleeding, which are not mutually exclusive, grouped into structural causes (PALM: Polyp, Adenomyosis, Leiomyoma (uterine fibroids), Malignancy and hyperplasia) and non-structural causes (COEIN: Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, Not otherwise classified) (fig 1).⁴ This allows a structured approach to be taken to investigation, diagnosis, and management in clinical practice.

How to approach a patient with abnormal uterine bleeding

It is important to establish the origin of the abnormal bleeding to ensure it is not from a non-gynaecological source and to rule out pregnancy.

Take a structured history,^{19 20} including frequency, duration, regularity, and flow volume, along with the presence of any intermenstrual bleeding, unscheduled bleeding on hormonal treatment, and associated symptoms such as pain or postcoital bleeding.^{1 2 4} Indications of AUB may include the presence of clots, presence of flooding (soaking through clothes while using menstrual products), changing menstrual products hourly or more frequently, and using double protection (using more than one menstrual product at a time).

Establish the effect that the bleeding has on a woman's quality of life by asking about avoiding wearing white or light-coloured clothes, leaving the house, or modifying their routine or having to take time off work while menstruating.

Take a routine gynaecological and medical history, including cervical screening, medication history, risk factors for endometrial hyperplasia or endometrial cancer (as AUB is an important sign of malignancy (box 1)), and any relevant family history. Cervical cancer may present with irregular bleeding that can easily be missed without appropriate history taking and pelvic examination.

Structured screening questions can be used to identify patients with an underlying coagulation disorder (box 2) and have been shown to have a 90% sensitivity in detecting underlying clotting disorders.²

Finally, ask about systemic symptoms, especially those that could indicate iron deficiency or anaemia such as shortness of breath, chest pain, or fatigue.

Box 1 | Risk factors for endometrial hyperplasia and endometrial malignancy

- Age >45 years
- Nulliparity
- Polycystic ovary syndrome
- Unopposed oestrogen therapy
- Raised body mass index (especially when BMI >30)
- Diabetes
- Hypertension
- Tamoxifen
- Family history of breast, colon, or endometrial cancer

Worldwide, the prevalence of iron deficiency anaemia is 30% among menstruating women, with approximately double this number having iron deficiency without a drop in haemoglobin.^{21 22} It is the commonest micronutrient deficiency in the world, and up to 60% of women with heavy menstrual bleeding will have iron deficiency.²² Iron deficiency and iron deficiency anaemia are under-recognised and under-reported.

Offer examination before investigation, including a general physical examination to look for signs of systemic disease such as anaemia, thyroid disease, or polycystic ovary syndrome (signs might include, for example, acne or hirsutism); an abdominal exam for a bulky uterus or abdominal mass; and a speculum and pelvic examination in women to whom this is acceptable.^{1 17} An intimate pelvic examination may not be acceptable, for example, to women who have never been sexually active, adolescents, or those who are unable to tolerate such examination.¹³ If a cervical ectropion is seen on examination, continue further investigation to exclude other causes of intermenstrual bleeding, because an ectropion may coexist with other causes of AUB. Arrange colposcopy referral if any suspicious cervical features are seen.

Initial investigations

Request a full blood count and, if possible, ferritin, although the latter is not routinely recommended in all countries, including the UK. These tests will help to assess for anaemia and iron deficiency, especially in women with heavy menstrual bleeding, as many women will have a low ferritin without a drop in their haemoglobin.^{2 22} If the bleeding is very heavy or chronic (six months or more) then consider iron studies as well; it is possible to have low iron stores or low transferrin levels with a normal ferritin level as ferritin is an acute phase protein.²²

Box 2 | Screening assessment for a coagulation disorder in women with abnormal uterine bleeding (AUB). (Adapted from Shankar 2004¹⁸)

Initial screening for underlying disorder of haemostasis in patients with AUB. A positive screening result comprises any of the following

- 1 Heavy menstrual bleeding (HMB) since menarche (first menstruation)
- 2 One of the following:
 - Postpartum haemorrhage (bleeding of ≥ 500 mL after a vaginal delivery or ≥ 1000 mL after a caesarean delivery)
 - Surgical related bleeding
 - Bleeding associated with dental work (for example, a tooth extraction)
- 3 Two or more of the following:
 - Bruising 1-2 times per month, especially unexplained bruising
 - Nose bleeds 1-2 times per month
 - Frequent gum bleeding not related to gum disease
 - Family history of bleeding symptoms (for example, mother or sisters with HMB or mother or grandmothers needing a hysterectomy at a young age due to HMB)

In women who have other signs and symptoms of thyroid disease, such as change in weight, diarrhoea, constipation, palpitations, and lethargy, offer thyroid function tests.¹ Screening for chlamydia is appropriate in women who have intermenstrual bleeding, postcoital bleeding, abnormal discharge, or other risk factors.²

It is likely that a woman with a normal cycle frequency and duration is having ovulatory cycles.² When a woman's cycle is irregular or infrequent it is more likely that her cycles are anovulatory.² If there is an indication for measuring circulating progesterone levels, timing is crucial: measure levels seven days before the start of

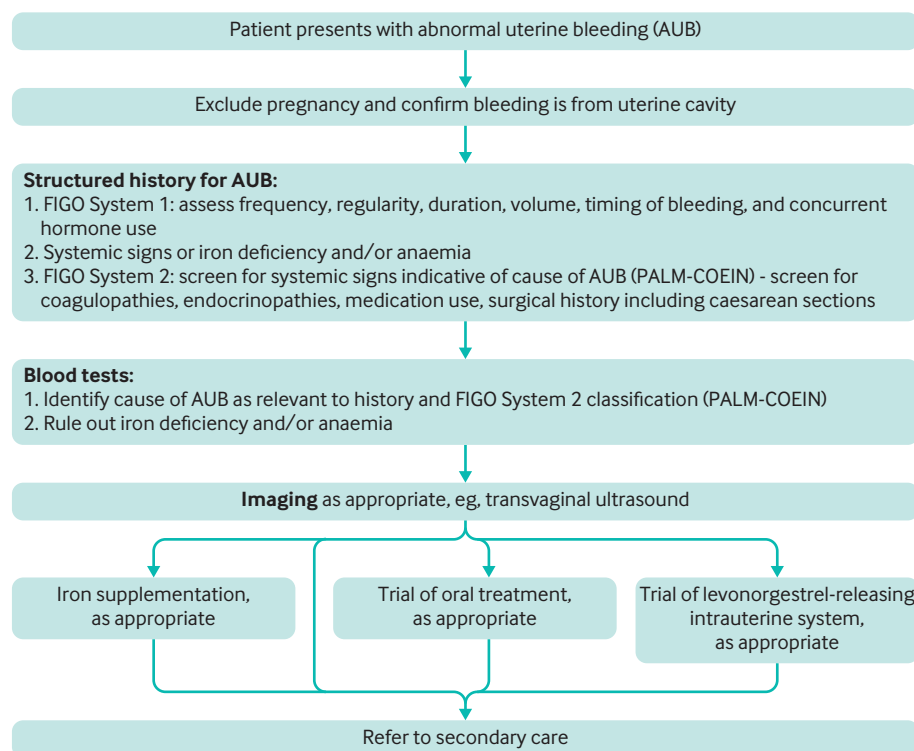
the woman's next cycle (that is, in a 28 day cycle, a day 21 level is appropriate, whereas in a 35 day cycle, a day 28 day level is appropriate). Consider measurement of serum prolactin, thyroid function tests, serum androgens (including testosterone, sex hormone binding globulin, free androgen index), follicle stimulating hormone and luteinising hormone to look for ovulatory causes of AUB.⁴

If the structured screening questions for coagulation disorders (box 2) are positive, then consider referral to a haematology department for testing for underlying coagulopathy.⁴

When to refer for further investigation?

If the woman is agreeable, a trial of medical therapy of 3-6 months without uterine evaluation may be appropriate for women who have: no risk factors for malignancy (box 1), a regular cycle, no intermenstrual bleeding, no pressure symptoms, no pelvic pain, have never had any previous treatment, no anaemia, and a normal examination.^{1,17} First line oral therapy is either tranexamic acid or mefenamic acid, prescribed singly or together for days 1-5 of the cycle.²³ Alternatively, consider a trial of the combined oral contraceptive pill if there are no contraindications and depending on patient preference.¹ The combined oral contraceptive pill can be tricycled (given continuously without a pill-free interval for up to three months) to avoid menstruation for two or three cycles if desired.

Tranexamic acid reduces blood loss by up to 50%, while mefenamic acid not only treats pain but has been shown to reduce blood loss by 25-50%.²³ If treatment fails, then continue to further investigation.



Box 3 | When to refer women with abnormal uterine bleeding (AUB) to secondary care

- Those who need an endometrial biopsy.
 - AUB and increased risk of endometrial hyperplasia or malignancy
 - Those taking hormonal contraceptive agents with a change in their bleeding pattern
- AUB and pressure symptoms from an abdominal mass
- Fibroids >3 cm diameter or distorting the endometrial cavity
- Abnormal ultrasound finding (such as a polyp or suspicion of endometrial hyperplasia or malignancy)
- If trial of 3-6 months of pharmacological agents to help AUB has not been helpful. Hormonal polytherapy should be limited to use in specific situations²⁴ (for example, to help problematic bleeding with a long-acting reversible contraceptive for up to 3 months) but it is ideally avoided long term
- AUB leading to anaemia
- Patients who wish to explore surgical options for their AUB or who request surgical or definitive management for their AUB

Fig 2 | Suggested investigation pathway when a patient of reproductive age presents with abnormal uterine bleeding in primary care. An understanding of FIGO systems 1 and 2 (see full article on bmj.com for details), as well as risks for endometrial hyperplasia or malignancy (box 1) and when to refer to secondary care (box 3) aid the use of this flowchart.

A PATIENT'S PERSPECTIVE

At 13 years old, I had the most embarrassing times because of my heavy bleeding. I would have to walk back home after flooding* down to my socks, so late for school. In assembly, I had to stay crossed legged on the floor as my clothes were flooded. Leaving the classroom very noticeably as a flood was coming. Sleeping on a pile of bath towels in case I flooded my bed. Always noticing an odour, so trying to avoid others and becoming a loner. I was very aware of problems disposing of underwear and towels and the embarrassment of trying to wash the blood from my clothes. Always aware that the lump of the sanitary towels showed through my clothes; therefore, I lost a lot of self-esteem and became isolated.

At 17 years old, I joined the army and the doctor put me on the contraceptive pill to help, and it was like a miracle: it gave me normal, light, easy periods.

The menopause was smashing, as I could not stay forever on the contraceptive pill.

Although I never had pain, I was never tested or investigated or checked for iron deficiency. My quality of life as a young, carefree female was certainly curtailed, and I became withdrawn and alone as a result of my heavy periods.

*Flooding is the presence of menstrual bleeding that is so heavy that it causes a person to bleed through their menstrual products and on to their clothes and beyond.

Treatment should take into account any comorbidities and the woman's preferences as well as her fertility aspirations

All other women should be investigated to identify a cause of the AUB. It is reasonable to offer a trial of oral therapy (as above) for symptom relief while a woman is undergoing investigation.

Pelvic ultrasound is the first line imaging investigation, ideally transvaginal, but this may not be appropriate in all women, especially adolescents and those who have never been sexually active.^{14 17} MRI is not routinely offered as a first-line diagnostic tool¹³; endometrial thickness in women of reproductive age is of limited value in detecting abnormalities, as it changes throughout the menstrual cycle.¹⁷

If the woman's history suggests malignancy or a polyp, consider an urgent direct referral for hysteroscopy. This includes women who have persistent intermenstrual bleeding, who have had treatment failure, or who are high risk for endometrial malignancy or hyperplasia (such as women taking tamoxifen).^{14 17}

For women who have uterine or cervical polyps, fibroids >3 cm diameter, or fibroids distorting the uterine cavity on ultrasound, offer referral to secondary care for further management. Urgently refer all women with evidence of malignancy or endometrial hyperplasia on ultrasound.

Pelvic ultrasound is not 100% sensitive.¹³ For women with risk factors for endometrial hyperplasia or malignancy (box 1), unexplained or persistent AUB, or for whom treatment has failed but who have a normal pelvic ultrasound scan, offer referral for endometrial sampling.^{2 17} Endometrial sampling should ideally be performed at hysteroscopy under direct vision if available.

See figure 2 for a suggested investigation pathway and box 3 for when to refer women to secondary care.

EDUCATION INTO PRACTICE

- What did you do the last time you saw a patient of reproductive age with increasingly heavy menstruation?
- How might you incorporate the PALM-COEIN classification of the causes of abnormal uterine bleeding into your diagnostic approach?

Management

Detailed management guidance is outside the scope of this article. However, treatment should take into account any comorbidities and the woman's preferences as well as her fertility aspirations. Common side effects should be discussed along with efficacy and any risks or benefits.¹

In women diagnosed with adenomyosis or AUB caused by endometrial factors after appropriate investigation, or in women with uterine fibroids <3 cm in diameter that are not causing distortion to the uterine cavity, medical treatment should be first line.¹ For this, NICE recommends a levonorgestrel-releasing intrauterine system (LNG-IUS).¹ Warn patients that it may take up to six months to be effective.¹ Up to 1 in 4 women experience persistent spotting at six months after insertion, but this falls to 1 in 10 at 24 months.²⁵ Rates of amenorrhoea at one year vary from 5.2% to 18.2%.^{26 27} The most common reasons for discontinuation of the LNG-IUS are prolonged or irregular bleeding and no improvement in symptoms.²⁸

If the LNG-IUS is not acceptable to the woman, then alternative first line oral therapy can be commenced, as described above.¹ The progestogen only pill may provide some symptom relief for women with heavy menstrual bleeding if oestrogen use is contraindicated,²³ although it is not licensed for treating heavy menstrual bleeding. Progestogens, such as medroxyprogesterone acetate (MPA) can help ease an acute bleed, but the patient should be counselled that this is not a contraceptive agent and she should expect a bleed approximately 48 hours after ceasing treatment. MPA from days 5-26 of each cycle may also be used to lighten menstruation and provide a predictable bleeding pattern.²³ Use of adjuvant tranexamic acid or mefenamic acid on days 1-5 of each cycle can further lighten menstruation for women using MPA cyclically.

Offer iron therapy to women who have iron deficiency or iron deficiency anaemia that does not warrant immediate transfusion.

Any surgical interventions should be discussed in a holistic manner with the woman, once she has been thoroughly investigated, bearing in mind her fertility aspirations. Abdominal hysterectomy and myomectomy are still management options, but they are by no means the only surgical options available. Hysterectomy and myomectomy can now be performed laparoscopically (dependent on uterine size), while less invasive management options include endometrial ablation, ultrasound-guided high-intensity transcatheter focused ultrasound for symptomatic fibroids, transcervical resection of fibroids, and uterine artery embolisation.

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ENDGAMES

CASE REVIEW

Bruise over the palm

A construction worker in his 50s was hit on his right hand by a metal pipe. He consulted his family doctor two hours later with diffuse pain of his right hand that was exacerbated by movement of his fingers. His right hand was swollen with a bruise on the palm. He had no history of coagulopathy and did not use anticoagulants. He was diagnosed with a soft tissue injury and treated with analgesics. However, as the pain increased and did not respond to analgesics, he went to his local emergency room five hours after the injury. On examination, the hand was swollen with extensive bruising over the palm. The radial and ulnar pulses were palpable. The fingers were flexed, and tactile sensation of the hand was intact. Passive extension, adduction, and abduction of all fingers exaggerated the pain. A radiograph showed fractures of the fourth and fifth metacarpals.

- 1 What is the most likely diagnosis?
- 2 What further investigations are required?
- 3 How would you manage this patient?



Clinical photos of the patient's right hand with extensive bruising of the palm (left) but not the back of the hand (right)

Submitted by Tun Hing Lui, Wah Bong Wong, and Xiaohua Pan

Patient consent obtained

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4-5 days can reduce the risk of infection. K-wires. Early closure of the fasciotomy wounds within muscles. The metacarpal fractures can be fixed with and prevent permanent damage to the nerves and fasciotomy can relieve intracompartmental pressure. Early be referred urgently to the orthopaedics team. The patient must impairment in tissue perfusion. The patient must injured hand should not be elevated to avoid further immediately, and the limb kept at the heart level. The All constricting material should be removed

PATIENT OUTCOME

- See bmj.com/endgames
- 3 How would you manage this patient?
- inconclusive.
- pressure may be relevant if the patient has impaired consciousness or the clinical examination is fasciotomy. Measuring intracompartmental pressure has been defined as an indication for
- may be measured. However, no absolute threshold pressure has been defined as an indication for
- If in doubt, intracompartmental perfusion pressure should not be delayed for this emergency condition. necessary for diagnosis, and surgical management grounds alone. Blood investigations are not as fasciotomy can be performed based on clinical further investigations are not usually required,
- 2 What further investigations are required?
- Compartment syndrome should be considered in patients with crush injuries and severe worsening pain
 - Diagnosis of compartment syndrome is usually clinical, and measuring intracompartmental pressure is not usually necessary

LEARNING POINTS

1 What is the most likely diagnosis?

Acute compartment syndrome of the hand secondary to a crush injury. Acute compartment syndrome is an orthopaedic emergency, with increased intracompartmental pressure leading to capillary collapse, perfusion shutdown, tissue hypoxia, and, finally, intracompartmental muscle and nerve death. It is mainly a clinical diagnosis, and the classic "6P" signs are pain, pallor, paresthesia, pulselessness, and paralysis. Increasing or disproportionate pain that increases with passive stretch muscles of the involved compartment is an early and hallmark sign and should not be attributed to an underlying fracture. Other signs are late and inconsistent. Waiting for development of these late presentation signs is impractical and will lead to permanent damage of the intracompartmental nerves and muscles and even limb loss.

In contrast to compartment syndromes at other sites, hand compartment syndrome generally lacks sensory deficits as no sensory nerves are located within the hand compartments. If paresthesia occurs, the carpal tunnel or ulnar canal may be involved.

CASE REVIEW Bruise over the palm

answers



You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.



Articles with a "learning module" logo have a linked BMJ Learning module at <http://learning.bmj.com>.

Unilateral beard

This is a Becker's naevus on the left chin of a man in his 20s.

The patient reported that a light tan patch had been present on the left side of his chin since childhood. The lesion was not associated with symptoms. When the patient's facial hair developed during puberty, he noticed it was thicker in the area of the patch and required more frequent trimming.

On examination, a well circumscribed hyperpigmented patch with hypertrichosis was noted in the left submandibular

region and left side of the neck, overlapping with the beard area. No facial asymmetry was evident. Becker's naevus was diagnosed.

Becker's naevus is a cutaneous hamartoma, characterised by localised, unilateral patchy brown hyperpigmentation with a well demarcated geographical border. Occasionally, as in this patient, hypertrichosis is also present. Becker's naevus is an androgen dependent lesion that occurs mostly in men,

although boys can also be affected. Although it typically develops on the upper trunk, it occasionally can be found elsewhere. Diagnosis is based on clinical findings.

Differential diagnoses include congenital melanocytic naevus, smooth muscle hamartoma, and post-inflammatory hyperpigmentation. Although Becker's naevus might lead to reshaping of the beard area if presented on the face, malignant transformation has not been reported.



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Patient consent obtained

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Diagnosing urinary tract infections in infants

Dipstick urine analysis is both sensitive and specific when used for diagnosing urinary tract infections in febrile infants aged less than 3 months. That's the conclusion of a study of 275 cases attending emergency departments in the UK and Ireland. The most sensitive individual dipstick indicator of urinary tract infection was the presence of leucocytes. The most specific indicator was the presence of nitrites (*Arch Dis Child* doi: 10.1136/archdischild-2022-324300).

Mask wearing for deaf people

Lip reading becomes impossible when people are wearing face masks. Sign language is compromised too, because facial expression is an important part of conveying meaning. In an essay in *The Atlantic*, a deaf person explains that, without lip reading, she couldn't wing it as a hearing person and even trivial encounters required her to explain her disability. On the plus side, she learnt to use smartphone apps with voice recognition and easy-to-read text displays (www.theatlantic.com/ideas/archive/2022/09/covid-deaf-mask-lipreading-sign-language/671398/).

In Europe older people with better educated children had higher quality of life scores and fewer depressive symptoms

Offsprings' education and parents' cognitive function

Studies from China and Mexico have found that people whose children have spent more years in school are less likely to show cognitive decline in old age. This might be because better educated children can help their parents financially or provide other sorts of support. By contrast, a European survey found only weak associations between cognition and educational level of children. However, older people with better educated children had higher quality of life scores and fewer depressive symptoms (*Am J Epidemiol* doi:10.1093/aje/kwac151).

Depression in people with diabetes

Electronic medical records of more than a million adults with type 2 diabetes diagnosed between 2006 and 2017 reveal increasing rates of depression at the time of diagnosis in all age groups. In the US, for example, the prevalence of depression rose from 29% in 2006 to 43% in 2017. People diagnosed with diabetes before the age of 40 were more likely to be depressed than those diagnosed later in life (*Diabetologia* doi:10.1007/s00125-022-05764-9).

Lifestyle intervention in older adults

On the subject of type 2 diabetes, a randomised trial in the US has found that lifestyle interventions are worth while in older patients. A year long programme involving weight reduction, dietary advice, and frequent sessions of supervised exercise

improved glycaemic control and reduced insulin requirements. Body weight and measures of visceral fat decreased in the intervention group. The main adverse effect was an increase in frequency of episodes of hypoglycaemia (*Diabetes Care* doi:10.2337/dc22-0338).

Clinical trial design

Organisers of randomised trials try to select participants at high risk of the outcome of interest within the duration of the trial. This makes for an efficient design but creates a problem when extrapolating from the trial results to the generality of patients. Among participants in a population based study in Denmark, less than half of those with chronic obstructive pulmonary disease would have been eligible for clinical trials when common inclusion criteria were applied (*Am J Respir Crit Care Med* doi:10.1164/rccm.202110-24410C).

Reducing waste

Endoscopy is one of the largest generators of medical waste. An initiative in one hospital shows that simple measures can have a useful effect. A brief intervention, consisting of education of endoscopy staff in the handling and segregation of waste and the relocation of recycling bins, led to a substantial reduction in the size of the carbon footprint left by endoscopic procedures. The benefits were sustained four months after the intervention (*Gut* doi:10.1136/gutjnl-2022-327005).

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