education

FROM THE JOURNALS Edited highlights of weekly research reviews on https://bit.ly/2PLtil8

Maternal covid-19

A nationwide Swedish cohort study found increased rates of some neonatal morbidities, including respiratory distress, with maternal covid-19. However, the increased risk was minimal, and, given the multiplicity of data (lots of outcomes were looked at), it's hard to know how genuine these findings are.

The authors looked at 88 000 infants, of whom 1.6% were delivered by mothers who tested positive for covid. Infants were matched by maternal characteristics, and the neonatal outcomes were compared between infants of covid positive and covid negative mothers. We do not know if covid-19 mediated the difference, or if it could have been due to the mothers with covid being treated differently, or that factors that made the women more likely to get covid also influenced the neonatal outcome. Generally these data are reassuring that covid-19 isn't upping neonatal risk too dramatically.

JAMA doi:10.1001/jama.2021.5775

Education to reduce upper GI endoscopies for dyspepsia

De Jong and colleagues randomised 119 patients with uninvestigated dyspepsia to health education or usual care. I find this interesting given that usual care would, I imagine, include a level of education, or at least explanation. A year on, the proportion of patients having upper GI endoscopies was 39% in the education group and 82% in the usual care group. This is an impressive fall in rates of a procedure with a low diagnostic yield (gastroscopy for dyspepsia) without compromising symptoms and quality of life.

The intervention was a web based tool with videos and 3D animations, so I wonder what other procedures this approach could be applied to. One slight caveat is that the results may only be generalisable to the type of patient prepared to participate in research. But even if there was some loss of effectiveness, it would still be worth implementing to avoid gastroscopies that are unlikely to benefit patients.

JAMA Intern Med doi:10.1001/jamainternmed.2021.1408

Sexual acceptability of contraception

Higgins and colleagues explored the association of sexual function, satisfaction, and self-reported sexual acceptability with continued contraception use over time in more than 2000 women in Utah. Contraception needs to be adhered to, so it's vital that factors affecting adherence are understood.

Interestingly, more than half of the women thought that the contraception had improved their sex life. Contraception making their sex life worse was strongly associated with stopping the contraception method at six months. Sexual acceptability turns out to be really important. This is therefore an important topic to cover in contraception decision making conversations—just as much as mood, weight gain, and blood pressure get covered.

JAMA Intern Med doi:10.1001/jamainternmed.2021.1439

Immunological intrigue with paediatric brain tumours

Immunovirotherapy seems to do something for high grade paediatric gliomas (a condition with poor survival) in a single arm trial of 12 patients. The therapy is a genetically engineered oncolytic herpes simplex virus (G207). It is designed to selectively infect and lyse tumour cells. It is also supposed to reverse tumour immune evasion. It is adminstered directly into the tumour and supplemented with radiation to enhance efficacy. The results of this phase I trial were favourable in terms of clinical response and safety. Hopefully, phase II will be promising too.

N Engl J Med doi:10.1056/NEJMoa2024947

Tranexamic acid for C section

In this trial, 4551 women undergoing caesarean delivery were randomised to tranexamic acid or placebo in a double blind fashion. The primary outcome was postpartum haemorrhage (defined as >1000 mL estimated blood loss or receipt of transfusion within two days of delivery). The trial showed that tranexamic acid reduced this primary outcome compared with placebo (26.7% versus 31.6%). But the haemorrhage related secondary outcomes (gravimetrically estimated blood loss, provider assessed clinically significant postpartum haemorrhage, use of additional uterotonic agents, and postpartum blood transfusion) were not reduced, which calls into question whether the treatment makes a clinically significant difference.

Thromboembolic event rates were very low but numerically higher in the treatment group. A quarter of participants did not receive the tranexamic acid or placebo within three minutes of delivery as required by the protocol—one of the realities of trial conduct. This probably wasn't the reason for a lack of greater efficacy, though. The resounding evidence for tranexamic acid that was expected (given that it is in widespread use) did not come.

N Engl J Med doi:10.1056/NEJMoa2028788

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Should all pregnant women be offered testing for group B streptococcus?

CPD READING
0.5 HOURS

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series advisers are Sera Tort, clinical editor, and Nai Ming Lai, clinical editor. You can read more about how to prepare and submit an Education article on our Instructions for Authors pages:https://www.bmj.com/about-bmj/resources-authors/article-types

Testing identifies nearly all pregnant women with GBS, but colonisation status may change

Introducing routine testing for group B streptococcus (GBS) for all women in late pregnancy would likely reduce cases of early onset infection in their newborns, but might also increase the number of women given antibiotics during labour.

One in five pregnant women carries GBS in the gut or genital tract, and more than half of them will pass it to their child during pregnancy, labour (most commonly), or after birth.[1] Most babies exposed to maternal GBS remain well, but one in 1750 newborns in the UK and Republic of Ireland develops early onset GBS infection, mostly pneumonia and sepsis. Each year in the UK about 40 babies die from GBS infection, and one in 14 of the survivors has a long term disability.[1] Babies born preterm are at higher risk of serious infection and death.[2]

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Jane Plumb of Group B Strep Support, who is integral to the GBS3 trial, recruited new and expectant parents to review an earlier version of this article. As a result of their input we re-wrote the section on what expectant parents need to know to make the language more understandable. Throughout the whole article, the disadvantages of testing methods were discussed.

WHAT YOU NEED TO KNOW

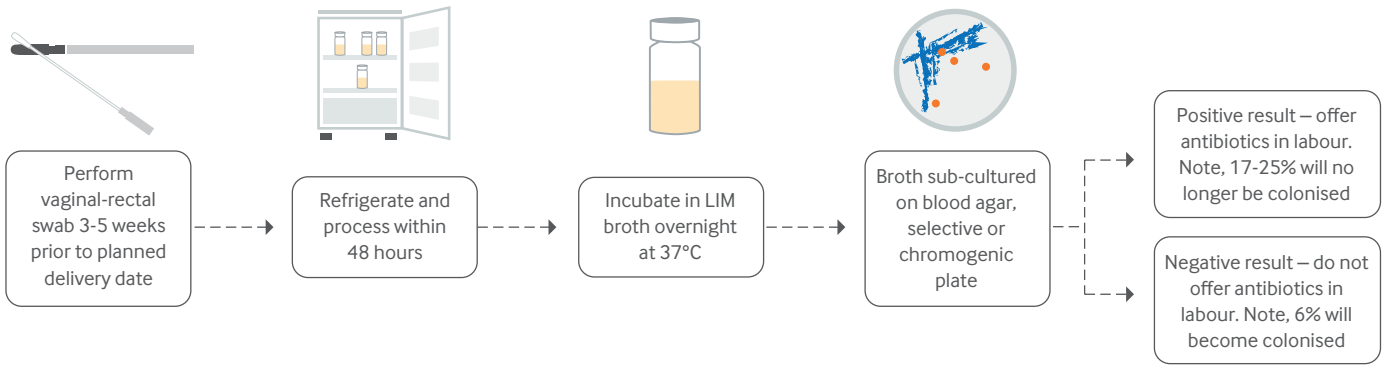
- Many countries have guidelines that recommend universal testing for group B streptococcus (GBS) in late pregnancy so that women who are colonised with GBS receive intrapartum antibiotic prophylaxis to prevent newborn GBS infection
- Observational studies suggest that routine testing in pregnancy reduces the risk of early onset GBS in newborns compared with offering antibiotics to women with risk factors for GBS transmission, or no testing. However, those observational studies have a moderate to critical risk of bias, and no randomised trials of routine testing versus a risk factor based approach have taken place
- Routine testing could result in a large number of women receiving antibiotics unnecessarily, resulting in potential harms of widespread antibiotic use at individual and population levels
- Offer testing for GBS carriage to pregnant women as per local guidelines, and where that guidance is lacking, discuss with the woman the risks and benefits of testing, as well as how the test result could affect her delivery

Low quality evidence shows that giving antibiotic prophylaxis to women known to be colonised with GBS during labour (intrapartum antibiotic prophylaxis, or IAP) reduces the incidence of early onset GBS infection in newborns. A Cochrane review of three randomised controlled trials (RCTs) (500 women, 488 babies) found that, compared with no treatment, giving antibiotic prophylaxis in labour to pregnant women known to be colonised with GBS was associated with a reduction in the incidence of early onset neonatal GBS infection (risk ratio (RR) 0.17, 95% confidence interval (CI) 0.04 to 0.74, risk difference -0.4, 95% CI -0.07 to -0.01), although all trials were at a high risk of bias. No differences in the incidence of late onset infection or infection from other organisms were observed.[3]

Two strategies are commonly used to identify which pregnant women need antibiotic prophylaxis to reduce early onset neonatal GBS infection. One approach is routine testing for GBS colonisation in all pregnant women, and the other is based on risk factors to determine which women should be offered antibiotics in labour.

Many countries, including the US and 34 others, test all women for GBS in late pregnancy and offer women who test positive antibiotic prophylaxis during labour (table 1, bmj.com).[4] Maternal GBS testing typically involves microbiological culture of a vaginal-rectal swab at 35-37 weeks' gestation (figure, p 200). The rationale for universal testing is that it identifies nearly all pregnant women with GBS colonisation at the time of testing. The downsides are that colonisation status may change between the time of testing and the time of birth, and maternal GBS colonisation alone does not mean that a baby will develop GBS infection.

By contrast, the UK National Screening Committee recommends against routine universal testing for maternal GBS colonisation. The potential harms from intrapartum antibiotics at an individual level (maternal adverse effects, childhood diseases linked to disruption of the microbiome) and at a population level (antimicrobial resistance) are unclear. Evidence consistently shows short term intestinal microbiota changes in infants born to mothers receiving prophylactic antibiotics in labour.[11] Gut dysbiosis may increase the risk of metabolic and autoimmune conditions, as seen experimentally in animal models.[12] The Royal College of Obstetricians and Gynaecologists recommends targeting the offer of antibiotic prophylaxis in labour to women who have risk factors for GBS transmission (box 1).[6]



Microbiological culture for GBS colonisation, with a two stage enrichment culture as the recommended method

And yet, an observational study in the UK and Republic of Ireland (including 794 037 live births in 2000 and 914 132 live births in 2014) reported a rise in the incidence of early onset GBS infections from 0.48/1000 births in 2000 to 0.57/1000 births in 2014-15,[13 14] despite the introduction of a national risk factor based prevention strategy in 2003. Over roughly the same time period in the US, where routine late third trimester testing was adopted in 2002, surveillance studies (encompassing 629 912 live births in 2002 and ≈200 000 live births in 2014) showed that the incidence of early onset GBS infection rates had decreased from 0.5 per 1000 live births in 1998-1999 to 0.22 in 2014.[15 16]

Uncertainty remains as to whether routine testing for GBS colonisation in late pregnancy or a risk factor based strategy for administering IAP strikes the best balance between preventing GBS transmission and the potential harms of antibiotic use.

Box 1 | Maternal risk factors known to increase the chance of a baby developing early onset GBS infection

- Preterm birth
- The mother has previously had a baby affected by GBS infection
- The mother has a fever or other signs of maternal infection during labour
- GBS detected from a vaginal or rectal swab or a urine sample taken from the mother during the current pregnancy
- Ruptured amniotic membranes more than 24 hours before the baby is born

However, not all of these risk factors prompt the offer of IAP in the UK. As per the 2017 guideline from the Royal College of Obstetrics and Gynaecology, the presence of any one of the following risk factors prompts the offer of IAP:

- Preterm labour
- The woman has previously had a baby affected by GBS infection
- Maternal fever or other signs of maternal infection during labour
- GBS detected from a swab or sample taken from the mother during the current pregnancy (eg, from a urine culture to investigate urinary symptoms or where a woman has chosen to test outside the NHS)
- GBS detected from a swab or sample taken from the mother in a previous pregnancy (in this situation, the mother should be offered the option of testing for GBS carriage using a GBS specific test with IAP offered if the result is positive, or being offered IAP without testing)

Although the mother's waters breaking more than 24 hours before the baby is born is recognised as a risk factor for early onset GBS infection, current guidelines do not recommend the automatic offer of IAP in this situation

What is the evidence of uncertainty?

Many observational studies have compared routine testing for GBS with a strategy based on risk factors, but no randomised controlled trials of universal routine testing have been conducted.

Three systematic reviews of observational studies completed in 2019-20 (11 million, 600 000 and 9828 live births, respectively) indicate that routine testing more than halved the risk of early onset GBS infection in newborns compared with risk factor directed antibiotic prophylaxis in labour. Similar numbers of women received antibiotics with either approach. Table 2 lists findings from these reviews.[17-19] No difference was seen in early onset GBS infection rates between risk factor directed protocols for giving IAP compared with no consistent IAP protocol.[17] Studies included in the systematic reviews were retrospective in design and noted substantial variations between testing protocols (timing of testing, site sampled, method of testing) and baseline rates of early onset GBS infections.

A 2016 modelling study commissioned by the UK National Screening Committee suggested that antenatal microbiological testing would correctly predict early onset GBS infection in around two of every 1000 pregnant women who tested positive for GBS colonisation,[1] meaning that 998 might have unnecessary antibiotics. Its further modelling suggested the proportion of women in labour receiving antibiotics would increase from 4.3% under a risk factor approach to 17.8% with routine testing. Routine testing would result in 1675-1854 additional women receiving IAP to prevent one neonate having early onset GBS infection.[20] The model's input parameters have subsequently been called into question, as the risk factor strategy emerged with an early onset GBS infection rate of 0.49/1000 live births, which is lower than what surveillance data suggest (0.57/1000).[2 20]

Without randomised controlled trial evidence, there is ongoing uncertainty regarding the balance of advantages and disadvantages of universal antenatal GBS testing compared with risk factor based strategies to identify pregnant women who should receive IAP to prevent GBS transmission to their babies.

Table 2 | Systematic reviews of observational studies of routine testing, risk factor directed intrapartum antibiotic prophylaxis, or no policy

Review	Comparison	Outcome	Number of studies (heterogeneity)	Relative risk (95% confidence interval)	Interpretation/limitations
Hasperhoven 2020 (17 studies, 11 million babies)[17]	Universal screening versus risk based policy	Early onset GBS infection*	10 (low)	0.43 (0.32 to 0.56)	Routine testing was associated with a reduction in cases of early onset GBS infection compared with a risk factor approach, while risk factor approaches could not show a significant benefit over no policy. The authors acknowledge substantial variations between testing protocols and baseline rates of early onset GBS infections
	Risk based policy versus no policy	Early onset GBS infection*	7 (high)	0.86 (0.61 to 1.20)	
	Universal screening versus no policy	Early onset GBS infection*	4 (high)	0.31 (0.11 to 0.84)	
Li 2020 (18 studies, 604 869 babies)[18]	Universal screening versus risk based screening	Early onset GBS infection†	18 (moderate)	0.45 (0.34 to 0.59)	Routine testing was associated with a reduction in cases of early onset GBS infection compared with a risk factor approach. Included studies used a retrospective design without parallel control and their quality was at a moderate to high level
Da Silva 2019 (2 studies, 9828 women)[19]	Universal screening versus no policy/ risk based screening	Neonatal infection‡	2 (none)	0.39 (0.17 to 0.91)	Routine testing was associated with a reduction in cases of early onset GBS infection compared with no policy. Limited number of included studies

*Positive GBS culture from normally sterile site, <7 days of age.
†Positive GBS culture from normally sterile site, or clinically defined sepsis or meningitis <7 days of age.
‡Not defined.

Is ongoing research likely to provide relevant evidence?

For the first time a randomised controlled trial comparing routine testing versus a risk factor based approach has been funded. The GBS3 trial (ISRCTN49639731) is a cluster randomised trial involving 320 000 women from up to 80 UK maternity units. It will determine the clinical and cost effectiveness of routine testing (160 000 women), compared with the current risk factor directed IAP strategy (160 000 women). There will also be a sub-randomisation to compare the testing strategies of antenatal enriched culture (80 000 women) at 35-37 weeks against intrapartum rapid testing (80 000 women). Recruitment has been delayed because of the covid-19 pandemic and will take two years. Simultaneous qualitative research will explore the factors that affect the adoption or uptake of either testing method, and a parallel economic evaluation will be undertaken. This RCT is likely to provide high quality evidence of the efficacy and cost effectiveness of IAP directed by universal testing compared with a risk factor based approach for preventing early onset neonatal GBS infection.

A separate UK based randomised trial compares the current practice of offering IAP to pregnant women with risk factors for GBS transmission without testing them with a strategy of offering these women intrapartum GBS testing, giving IAP only to women who test positive for GBS colonisation. This study will report its results in 2021 (ISRCTN74746075). No other trials are ongoing in this area from a search of ClinicalTrials.gov and ISRCTN registries performed on 9 March 2021 (box 2). Any maternal testing or risk factor based prevention strategy can—at best—identify women at risk of transmitting GBS to their babies. None can definitively predict which babies will develop GBS infection.

Box 2 | Search strategy

We searched PubMed in March 2021 using the terms "Group B streptococcus" OR "GBS" AND "screen" OR "screening" OR "test" OR "testing" OR "risk factor" NOT "Guillain-Barré syndrome", filtered on "systematic review" OR "meta-analysis" OR "randomised controlled trial" and limited to publications since May 2015. This yielded 60 results, including three systematic reviews of screening for GBS from 2019 to 2020[13-20] and one diagnostic test accuracy review of molecular testing methods, which was included in this article.[12] The 2016 review of the National Screening Committee criteria and outputs from the British Perinatal Surveillance Unit provided further information.[1-18]

What should we do in light of the uncertainty?

We recommend following existing guidelines that support either an institutional or national antenatal testing programme, or a risk factor based strategy. Patients may have questions about GBS testing and prophylaxis. Explain to women the potential advantages and disadvantages of routine testing for GBS (advantage: observational studies reporting a reduction in cases of newborn GBS infection; disadvantage: a large number of women requiring antibiotics in labour to prevent a small number of infections; the implications of widespread use of antibiotics; the implications of knowledge of colonisation status on choice of birth location).

Discuss their risk factors (box 1) and the testing options available to enable women to make informed and supported decisions about their care. Offer intrapartum antibiotic prophylaxis to women who are in preterm labour, have an intrapartum fever, where GBS has been detected in this or a previous pregnancy, or who have had a previous baby with GBS infection.[6]

Competing interests: See bmj.com.
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EDUCATION INTO PRACTICE

Think about the last time you talked to a pregnant woman about GBS. How confident did you feel answering her questions? How might you engage with women on this subject next time? How do you present GBS testing to women? Do you offer women a choice? What risks and benefits of testing might you discuss?

Investigating hypothyroidism

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CPD READING
0.5 HOURS

LEARNING MODULE
See http://learning.bmj.com for linked learning module

A 52 year old woman presents to her general practitioner with fatigue. She started to notice feeling tired more easily and getting more sleepy during the day about eight months ago and thinks it is worsening. She also notes that she has gained 10 lbs over the past year, without major changes in her diet or exercise. Her review of symptoms is positive for constipation and increased hair loss. Her medical history includes obesity, hypertension, hyperlipidaemia, and type 2 diabetes, although her hypertension and type 2 diabetes have been well controlled on medications. Her medications are lisinopril, atorvastatin, and metformin. Recent laboratory tests—including a full blood count, renal function panel, liver function panel, and plasma glucose—were normal. Physical examination is notable for normal vital signs, abdominal adiposity, and dry skin, but is otherwise unremarkable.

The patient notes that her mother had hypothyroidism, and she wonders if she should be tested.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

While creating this article, we reviewed a survey evaluating patient satisfaction with the treatment of their hypothyroidism.[23] Hypothyroidism has a significant effect on the lives of patient responders, 14-20% of whom were dissatisfied with their treatment and continued to experience symptoms of hypothyroidism while on medical therapy. When responders were asked to rate their satisfaction with their treatment on a scale of 1 to 10 (1=not satisfied, 10=very satisfied), the median reported satisfaction score was 5.[23] Recognising the significant effect that hypothyroidism can have on patients' quality of life and the ways that patients' experiences with hypothyroidism may be more complex than clinicians appreciate, we included specific guidance on how to counsel patients about their symptoms and diagnosis.

WHAT YOU NEED TO KNOW

- Suspect hypothyroidism in patients with convincing symptoms and/or signs, especially if they have risk factors for hypothyroidism, and refer them for thyroid stimulating hormone (TSH) measurement
- An elevated serum TSH and a low serum free thyroxine are diagnostic for primary hypothyroidism, and levothyroxine, adjusted every 4-6 weeks until TSH normalises, is the treatment of choice
- Universal screening for hypothyroidism is not recommended, as it may result in overdiagnosis, unnecessary treatment, and increased healthcare costs

Background

Hypothyroidism can be difficult to diagnose, as its signs and symptoms are non-specific, and no global consensus exists on screening. It can be difficult to determine when to test for hypothyroidism, as patients may present with symptoms that are subtle or that overlap with other common conditions, and guidelines can be vague regarding who and when to test. However, identification of overt hypothyroidism is important as, if left untreated, it can cause uncomfortable symptoms as well as increased risk for cardiac dysfunction, hypertension, dyslipidaemia, cognitive impairment, complications in pregnancy, and in rare cases, myxoedema coma.[1] While professional organisations generally recommend against universal screening for hypothyroidism, discrepancy exists and guidelines remain vague about who to test, generally recommending consideration of testing in patients for whom there is high clinical suspicion of the disease or in populations at increased risk, although they do not always define these populations. The broad nature of the guidelines reflects the wide range of ways this disease may present and who is likely to develop it (table). In countries that are iodine sufficient, the prevalence of overt hypothyroidism ranges from 1% to 2%, rising to 7% in older adults.[5] Hypothyroidism is approximately 10 times more common in women than in men.[5]

Guidelines for screening for hypothyroidism

Society	Recommendation
American Association of Clinical Endocrinologists	Recommendation for aggressive case finding in patients most likely to have thyroid disease (box 1) that will benefit from its treatment[2]
Canadian Task Force on Preventive Health Care	Strong recommendation against screening for thyroid dysfunction in asymptomatic, non-pregnant adults[1]
National Institute for Health and Care Excellence (NICE)	Consider tests for thyroid dysfunction when thyroid disease is clinically suspected, but bear in mind that one symptom alone may not be indicative of thyroid disease. Offer testing to people with type 1 diabetes mellitus or other autoimmune diseases, or new onset atrial fibrillation. Consider testing in people with depression or anxiety[3]*
United States Preventive Services Task Force	Concludes that evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in asymptomatic, non-pregnant adults[4]

*In NICE recommendations, the word "consider" is often used where the benefit is less certain, whereas "offer" is used where there is clear and strong evidence of benefit

Box 1 | Risk factors for hypothyroidism

- Iodine deficiency[5]
- Female sex[5]
- Age >65 years[6]
- Personal or family history of autoimmune disease (eg, type 1 diabetes mellitus, Addison's disease, coeliac disease)[7]
- Family history of thyroid disease[6]
- Positive thyroid peroxidase (TPO) antibodies[7]
- Medications including lithium, amiodarone, interferon alpha, interferon gamma, immune checkpoint inhibitors, or tyrosine kinase inhibitors[56]
- Prior surgery or radiation therapy on the thyroid gland, head, or neck area[6]

When to suspect hypothyroidism

Suspect hypothyroidism in patients with suggestive symptoms, examination findings, and laboratory abnormalities, particularly if they have risk factors such as those listed in box 1.

Symptoms are non-specific and most commonly include fatigue, shortness of breath, cold sensitivity, weight gain, constipation, change in voice, and dry skin.[6] Hair loss, menstrual irregularities, impaired memory, and depression may be seen as well.[167] Time course of symptom development and the number of symptoms that patients with hypothyroidism experience can vary greatly from one individual to another. Symptoms usually appear slowly over months or years, although may develop more quickly. Development or worsening of several of these symptoms increases the likelihood of hypothyroidism, compared with the development or presence of a single symptom,[6] and should prompt consideration of testing. However, some patients with hypothyroidism present with isolated symptoms or are asymptomatic.[1] This is particularly common in older patients, for whom you may consider a lower threshold to test for hypothyroidism.[8]

On examination, patients may have cool, dry, or coarse skin, yellowed palms, periorbital oedema, puffy face, peripheral oedema, enlarged tongue, and/or goitre.[6] Examination may reveal delayed relaxation of deep tendon reflexes.[6] Vital signs may reveal bradycardia or diastolic hypertension.[6] More severe hypothyroidism may present with pleural effusions, pericardial effusion, or ascites.[6] These findings are not present in all patients with hypothyroidism, but their presence should heighten suspicion for the disease. Dry skin has been noted to be a sensitive finding for hypothyroidism, although it may be present in euthyroid patients as well.[8] The other findings may be more specific and should prompt consideration of testing for hypothyroidism.

Laboratory abnormalities, including macrocytic anaemia, hypercholesterolaemia, hyponatraemia, and elevated creatine kinase, may suggest hypothyroidism as well.[69]

Pursue confirmatory testing in patients with signs or symptoms of hypothyroidism, with a lower threshold to test those with risk factors described in box 1. Other special populations who may benefit from a lower threshold for testing are described in box 2. Routine screening is not recommended, as it may result in unnecessary treatment in patients who have only transient laboratory abnormalities or abnormalities that may not reflect clinically significant thyroid dysfunction, over-testing and increased stress for patients, and increased healthcare costs.[1]

Box 2 | Special populations

Patients who are pregnant, planning pregnancy, affected by infertility, or postpartum

- Untreated hypothyroidism during pregnancy may adversely affect maternal and fetal outcomes. Routine screening of pregnant patients remains controversial. Follow local guidelines, and where absent, consider aggressive case finding in this population[10]
- All women seeking care for infertility warrant evaluation for hypothyroidism. In cases of overt hypothyroidism, treatment may restore normal fertility[10]
- For women planning conception but without a history of infertility, thyroid disease, or known thyroid antibody positivity, we recommend testing patients with signs, symptoms, or risk factors for hypothyroidism, but do not recommend routine screening[10]
- Postnatally, women may develop postpartum thyroiditis (PPT), which can include a thyrotoxic phase followed by a hypothyroid phase. Maintain a high level of suspicion for thyroid dysfunction in patients in the postpartum period, and check TSH level if symptoms (including depression) arise.[10] Women with a history of PPT should have a TSH level measured annually, as up to half of patients in whom the hypothyroid phase of PPT initially resolves go on to develop permanent hypothyroidism[10]

Patients with type 1 diabetes mellitus

- Approximately 10% of patients with type 1 diabetes mellitus develop chronic thyroiditis in their lifetime, which may lead to hypothyroidism.[7] Monitor patients with type 1 diabetes for signs or symptoms of hypothyroidism, and follow local guidance regarding regular TSH monitoring, typically annually[11]

Patients with Down's syndrome

- Patients with Down's syndrome have a higher prevalence of autoimmune thyroid disease compared with the general population, with thyroid autoantibodies being found in 13-34% of patients with Down's syndrome.[12] Patients may develop hypothyroidism in childhood or adulthood. Check TSH annually in adult patients with Down's syndrome[12]

Patients with new hyperlipidaemia

- Hypothyroidism can be a secondary cause of hyperlipidaemia. Check a TSH level in patients with hyperlipidaemia, particularly in those who are young adults (20 to 39 years) or have had substantial increases in their lipid measurements

Patients with depression or dementia

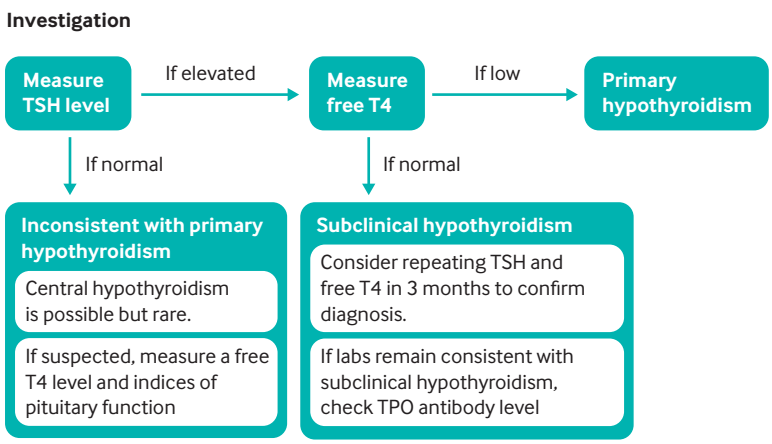
- Hypothyroidism can cause neurological and psychiatric symptoms that overlap with symptoms of depression and dementia. While there is some controversy regarding their potential associations, consider hypothyroidism in patients with depression and dementia[67]

Patients with obesity

- Hypothyroidism is found in approximately 14% of patients with obesity[13] and may potentiate weight gain and comorbidities associated with obesity. This has led some guidance associations to recommend screening for hypothyroidism in obese patients[13]

Patients taking certain medications

- Patients taking medications including lithium, amiodarone, tyrosine kinase inhibitors, multikinase inhibitors, and immune checkpoint inhibitors should undergo periodic evaluation of their thyroid function. Thyroid function should be checked every 4-6 weeks for the first six months after initiation of immune checkpoint inhibitors or kinase inhibitors and at least every three months subsequently; every 6-12 months for other medications[5671415]



Investigation of suspected hypothyroidism

What is the next investigation?

Serum TSH

If hypothyroidism is suspected, measure a serum concentration of TSH. A TSH elevated above the upper reference limit can represent either overt hypothyroidism, in which the levels of circulating thyroid hormones are low, or subclinical hypothyroidism, a milder degree of thyroid dysfunction in which circulating levels of thyroid hormones remain within normal limits.

The upper limit of normal for TSH has conventionally been set at 4.5-5 mU/L, although this varies based on laboratory reference limits. The normal range may widen with increasing age, and some experts suggest using age specific ranges for TSH to avoid overtreatment and its associated risks in older patients.[6]

Free thyroxine (T4)

If the TSH is elevated, check a free T4 level to help differentiate overt hypothyroidism from subclinical hypothyroidism. Note that some laboratories will reflexively measure a free T4 if TSH is abnormal or will measure both TSH and free T4 simultaneously.

How should I interpret the test results?

An elevated serum TSH and a low serum free T4 are diagnostic for primary hypothyroidism. An elevated TSH and a free T4 within normal range indicates subclinical hypothyroidism, a milder degree of thyroid failure (figure).

HOW THIS ARTICLE WAS MADE

We performed a literature review for this article using search terms including "hypothyroidism," "guidelines," "hypothyroidism screening," "thyroid screening guidelines," "thyroid screening guidelines primary care," "clinic hypothyroidism," "ATA," "AACE."

Other considerations

Subclinical hypothyroidism

If initial evaluation is consistent with subclinical hypothyroidism, it is reasonable to re-check the TSH and free T4 in three months. If evidence of subclinical hypothyroidism persists, check a TPO antibody level to predict the likelihood of progression to overt hypothyroidism. In people with subclinical hypothyroidism who have positive TPO antibody titres, 4.3% go on to develop overt hypothyroidism each year, compared with 2.6% of people with subclinical hypothyroidism but negative TPO antibody titres.[16] For patients with subclinical hypothyroidism who do not opt for treatment, TSH should be checked periodically and if new symptoms arise, to assess for potential progression to overt hypothyroidism which would require treatment. Patients with subclinical hypothyroidism and positive TPO antibodies should be monitored more closely, with TSH checked every 6-12 months. Note that in some patients with subclinical hypothyroidism, TSH will normalise spontaneously.[17]

When might an elevated TSH be a false positive?

While an elevated TSH is often a key finding in hypothyroidism, TSH may be elevated in other situations including in the recovery phase of non-thyroidal illness (eg, sick euthyroid syndrome),[6] the recovery phase of subacute or silent thyroiditis, and more rarely, in adrenal insufficiency, TSH secreting pituitary tumours, or resistance to thyroid hormone.[67] TSH may also be falsely elevated in the presence of heterophilic or interfering antibodies (eg, rheumatoid factor).[7]

Interpret an elevated TSH in the clinical context: if a patient with mildly elevated serum TSH has recently been ill, or if the patient is no longer having convincing symptoms of hypothyroidism, it may be reasonable to repeat TSH testing in 2-3 months to confirm the diagnosis before starting treatment.

What about false negative TSH results?

Normal TSH in the setting of hypothyroidism may occur in several instances. First, in central hypothyroidism, TSH secretion from the pituitary gland does not increase appropriately as T4 secretion falls. This is rare, but if a patient has convincing symptoms of hypothyroidism despite a normal TSH, measure a free T4 level, assess for symptoms that may suggest pituitary disease (eg, headaches, visual field disturbance, menstrual or sexual dysfunction, signs and symptoms of adrenal insufficiency), and consider measuring indices of pituitary function.

Additionally, TSH may be falsely low in patients who take supplemental biotin, as biotin can interfere with some immunoassay platforms.[18] Inquire about biotin use at the time of testing in patients with convincing signs or symptoms of hypothyroidism and a normal TSH, and ask patients to stop biotin supplements for several days before thyroid function testing.

Unnecessary tests

Checking the serum TPO antibody titre can help predict the likelihood of developing overt hypothyroidism in patients with subclinical hypothyroidism. However, it is not necessary to check thyroid antibody levels in patients with overt primary hypothyroidism if this would not change management. TPO antibodies do not need to be re-tested, either before or after starting treatment.

No evidence supports measuring total or free serum triiodothyronine (T3) or reverse triiodothyronine (rT3), an inactive metabolite of T4, when testing for hypothyroidism in a clinical setting.[19]

Thyroid ultrasound should only be performed if the patient has a goitre or palpable nodule, not as a routine part of the investigation for hypothyroidism. Incidentally discovered thyroid nodules are common, and overuse of ultrasound will frequently identify nodules that are unrelated to any abnormal thyroid function.[20]

Management

Treat patients with biochemical evidence of hypothyroidism with levothyroxine monotherapy.[21] Re-check the TSH level 4-6 weeks after starting treatment, and adjust the levothyroxine dose by 12-25 µg/day, allowing another 4-6 weeks to elapse before re-checking thyroid function, until the serum TSH normalises (evidence does not support targeting specific TSH values except in pregnant women or patients with a history of thyroid cancer, in whom the goal TSH may be lower).[21]

Treatment of subclinical hypothyroidism is more controversial. Different organisations recommend different TSH cut-offs for treatment, taking into consideration age, presence of TPO antibodies, plans for pregnancy, and presence of or risk factors for cardiac disease.[7]

Consider other potential causes for symptoms that do not improve despite biochemical correction of TSH with levothyroxine, with a low threshold for referring these patients to secondary care.[22]

Outcome

Given this patient's symptoms, physical examination findings, and risk factors for thyroid disease, a TSH level is measured and is 12.7 mU/L (normal range 0.4-4.0 mU/L). Free T4 level is found to be 0.5 ng/dL (6.4 pmol/L) (normal range 0.8-1.7 ng/dL, 10.3-21.9 pmol/L). These results are consistent with overt primary hypothyroidism. The patient is started on an initial weight-based dose of levothyroxine and her dose is adjusted every 4-6 weeks until her TSH normalises. Six months after her TSH normalises on levothyroxine, the patient reports improvement in her energy level and constipation, but continues to be concerned about her weight and her hair loss. Unfortunately, it is not uncommon for some symptoms to persist despite biochemical correction of hypothyroidism. The patient continues to work with her general practitioner to identify other potential causes and interventions for these continued symptoms.

DISCUSSING THE DIAGNOSIS WITH PATIENTS BEFORE AND AFTER TESTING

- Before testing for hypothyroidism, discuss the risks and benefits with patients. Counsel patients that they may require follow-up blood tests and that testing may not yield a definitive explanation for their symptoms. Discuss that even if the test is consistent with hypothyroidism, treatment with levothyroxine may not resolve all of their symptoms. Provide reassurance that you will continue to work with the patient to address their symptoms and concerns.
- In cases of biochemically confirmed hypothyroidism, discussing the diagnosis is relatively straightforward. Patients may feel relieved to have a clear diagnosis and a treatment to alleviate their symptoms
- Discussing a diagnosis of subclinical hypothyroidism may be less straightforward, as the recommendations regarding treatment vary. The decision of whether to treat may depend on the degree of TSH elevation, patient age, presence of convincing symptoms of hypothyroidism, and in women, the presence of infertility or plans for pregnancy. Clinicians should communicate openly with patients regarding the uncertainty in treating this condition and should use shared decision making to decide how to proceed
- Some patients with symptoms suggestive of hypothyroidism but no biochemical evidence of hypothyroidism may be disappointed not to have a clear explanation for their symptoms
- Using levothyroxine to treat symptoms in the absence of clear biochemical evidence of hypothyroidism is not indicated. Clinicians should explore other potential causes for patient symptoms, if investigation for hypothyroidism is negative
- As with all medical conditions, good communication and shared decision making between patients and clinicians is important when investigating and treating hypothyroidism. Additionally, patients may benefit from being directed to reliable websites and resources, such as the British Thyroid Foundation (www.btf-thyroid.org), the American Thyroid Association (www.thyroid.org), the European Thyroid Association (www.eurothyroid.com), or Choosing Wisely Canada Endocrinology (https://choosingwiselycanada.org/endocrinology-and-metabolism/), endorsed by the Canadian Society of Endocrinology and Metabolism, for further information and support around hypothyroidism

RATIONAL TESTING IN PRACTICE

- What is your threshold for testing patients with non-specific symptoms of hypothyroidism? Are there any pre-existing conditions that would make you more likely to test for hypothyroidism?
- How often in the past 12 months have you added a TSH "just in case," because of vague symptoms?
- Think about the last time you diagnosed someone with hypothyroidism. What clinical clues led you to the diagnosis?

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.n993

SPOT DIAGNOSIS

Hypopigmented atrophic plaques in a young woman

A woman in her 20s presented to dermatology clinic with a four year history of a mildly itchy hypopigmented patch in her natal cleft, and similar itchy lesions that had gradually appeared on the back of both knees over the past six months (fig 1, fig 2). The lesions ranged from white to brown.

Treatment with topical antifungal creams for suspected candidal intertrigo was unsuccessful.

Cutaneous examination revealed multiple ill defined hypopigmented plaques in the upper part of the natal cleft and both popliteal fossae. On close inspection, the affected skin showed fine wrinkling and increased translucency (not clear in the figure) indicating that the plaques were atrophic. The patient's genitalia and oral mucosa were unaffected.

We were unable to determine the presence of the Koebner phenomenon—the formation of new lesions on previously injured skin.

Because of the long history and atypical presentation, a skin biopsy sample was taken from the popliteal area. Histology showed compact orthohyperkeratoses, epidermal atrophy, basal cell vacuolation, subepidermal oedema and homogenisation of collagen, and a perivascular and periappendageal lymphohistiocytic infiltrate in the mid and lower dermis.

Thyroid function test results were within normal limits.

What is the most likely diagnosis?

Submitted by Prateek Sharma and V Ramesh

Patient consent obtained.

Cite this as: *BMJ* 2021;373:n1012

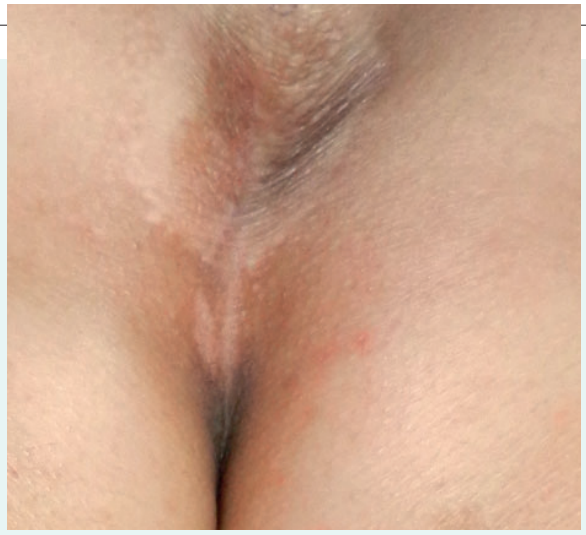


Fig 1 | Hypopigmented atrophic plaques in upper part of natal cleft

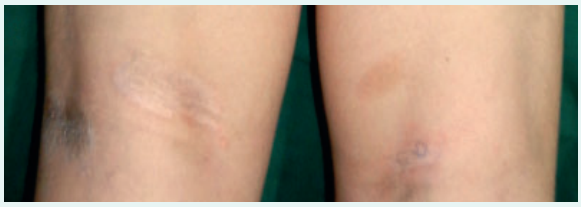


Fig 2 | Hypopigmented atrophic plaques in popliteal fossae

answers

SPOT DIAGNOSIS **Hypopigmented atrophic plaques in a young woman**

What is the most likely diagnosis?

Extragenital lichen sclerosus—suggested by the non-response to anticandidal treatment, atrophic hypopigmented plaques, and characteristic histopathology (orthohyperkeratosis, epidermal atrophy, basal cell vacuolation, subepidermal oedema and homogenisation of collagen, and a perivascular and periappendageal lymphohistiocytic infiltrate in the mid and lower dermis).

Lichen sclerosus typically presents as ivory white atrophic plaques (usually asymptomatic; occasionally pruritic) on the upper trunk, axillae, buttocks, and lateral thighs. In patients with darker skin tones, lesions are hypopigmented but might still be brown.

Koebner phenomenon is often present with extragenital lichen sclerosus, although it was not apparent in this case.

Extragenital lichen sclerosus might also be associated with plaque type morphea, which was not present in this case.

Vitiligo—the most likely differential—presents as asymptomatic or non-pruritic hypopigmented or depigmented patches, but without cutaneous atrophy. It can be difficult to differentiate from early cases of lichen sclerosus, when there is little atrophy.

Other differentials (excluded by histopathology) include morphea, erosive lichen planus, candidal intertrigo, and chronic graft versus host disease.

Thyroid function tests were done because autoimmune thyroid disease has been associated with lichen sclerosus.

Lichen sclerosus usually affects the anogenital skin (85-98% of cases), where it causes intense itching that might lead to bruising and secondary bacterial or fungal infection. Chronic or recurrent genital lichen sclerosus develops into squamous cell carcinoma in 3-5% of cases. Extragenital lichen sclerosus has no known malignancy risk, however.

It does not resolve spontaneously but usually responds well to topical application of potent steroids.

Recurrent and longstanding lesions might lead to patients having problems with self-image.

Monitor for treatment response and complications, according to local protocol.

PATIENT OUTCOME

The patient was prescribed clobetasol propionate 0.05% ointment and reviewed monthly. After the first few visits, skin texture had improved and the patient reported better satisfaction. The patient was lost to follow-up, however, so long term outcome could not be ascertained.

LEARNING POINT

Consider extragenital lichen sclerosus as a differential when patients present with areas of hypopigmentation.

CPD READING 0.5 HOURS

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

LEARNING MODULE

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

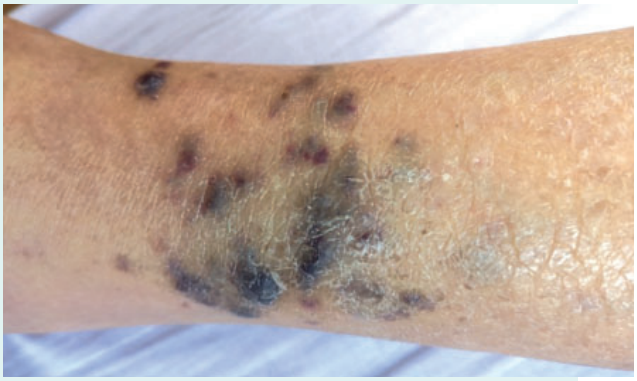
MINERVA

Cutaneous Kaposi's sarcoma

This is iatrogenic Kaposi's sarcoma associated with human herpesvirus 8 on the leg of a woman in her 60s.

One year earlier she had received a diagnosis of dermatomyositis, an autoimmune inflammatory myopathy. She was treated with prednisolone and cyclosporin. During treatment she presented with extensive, raised, firm, purple-black nodules on her face, chest, back, and limbs. Scaling and necrosis were seen on macro lens (a magnifying lens used for dermatological photography). The test result for HIV was negative and no evidence of visceral involvement was observed on imaging. Skin biopsy and immunohistochemical staining confirmed a diagnosis of Kaposi's sarcoma.

Iatrogenic Kaposi's sarcoma caused by immunosuppressants occurs because of weakened immunological surveillance, which reactivates latent human herpesvirus 8 infection and contributes to the proliferative transformation and angiogenic properties of the infected endothelial cells. Kaposi's sarcoma should be considered in people with immunosuppression who present with such a rash.



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Patient consent obtained.

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If you would like to write a Minerva picture case, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx

Measuring heart failure

The New York Heart Association system divides heart failure into four classes of severity, based on clinician assessment. The Kansas City Cardiomyopathy Questionnaire, by contrast, is a 23 item, self-administered inquiry about physical and social functioning, symptoms, and quality of life. A study of 3000 people with chronic heart failure shows that the latter is a more sensitive measure. Over 12 months, 75% of patients showed a change of five points or more in the Kansas City Cardiomyopathy Questionnaire, while only 35% changed New York Heart Association class (*JAMA Cardiol* doi:10.1001/jamacardio.2021.0372).

Mutations and variants

SARS-CoV-2 variants are complicated, each made up of a collection of mutations, any of which can change the virus in unexpected ways. Minerva enjoyed a short video produced by *Nature* (doi:10.1038/d41586-021-00993-1) which explains why variants matter, how they spread, and what they might mean for the future of the pandemic. Monitoring the emergence of new variants will be an important part of coping with the virus.

People who slept less than six hours a night in middle age were 30% more likely to develop late onset dementia

Declining androgen levels

A longitudinal study of healthy men found that androgen levels start falling early during adult life. The decline occurs independently of changes in weight, body mass index, and lifestyle factors. Falling androgen concentrations are accompanied by a rise in gonadotropin levels, which suggests that the primary cause is diminishing testicular function (*J Clin Endocrinol Metab* doi:10.1210/clinem/dgaa915).

Generalising from trial results

Although clinical trials generate high quality evidence, it's sometimes hard to know if the findings are generalisable. A study from a medical centre in the US finds systematic differences between people taking part in trials and patients who weren't involved. Trial participants had less comorbidity and took fewer medications (*JAMA Netw Open* doi:10.1001/jamanetworkopen.2021.4732).

Infection rates and masks ...

An ecological study from the US—where policies on mask wearing have varied from state to state during the pandemic—reports that places with high rates of mask wearing have lower rates of SARS-CoV-2 infection. Of 15 states that did not require people to wear masks in public, 14 had high rates of covid-19 infection. On the other hand, none of the eight states in which compliance with mask wearing was better than 75% had high covid-19 rates (*PLOS ONE* doi:10.1371/journal.pone.0249891).

... and where to wear them

Now that more is known about the transmission of SARS-CoV-2, it's worth reconsidering which aspects of public health advice should be reinforced and which should be abandoned. An infectious disease expert argues that it's time to stop telling people to wear masks outdoors. Little or no transmission happens in the open air, and encouraging mask wearing outside will mislead people about how the virus is spread (https://blogs.jwatch.org/hiv-id-observations/index.php/is-it-time-to-eliminate-outdoor-mask-mandates/2021/04/19/).

Sleep duration and dementia

In the long running Whitehall II study, people who slept for less than six hours a night in middle age were about 30% more likely to develop late onset dementia than those who slept for seven hours. The increased risk was present even after taking account of sociodemographic and mental health variables. Risk of dementia was also raised in people who slept for more than eight hours a night, although too few people came into this category for the finding to be considered robust (*Nat Commun* doi:10.1038/s41467-021-22354-2).

Cite this as: *BMJ* 2021;373:n1101