education

FROM THE JOURNALS Edited highlights of weekly research reviews

Spare the tonsils?

I'm from a generation whose tonsils and adenoids were whipped out at the first hint of snuffles or sore throats. In the UK, the pendulum has swung towards a more rational approach, which means tonsillectomy and adenoidectomy have become relatively rare procedures. This large retrospective cohort study of over half a million children (median age 7 years) in five US states reminds us that no operation is ever without risk.

The postoperative death rate within 30 days of tonsillectomy was 7/100 000 overall and 117/100 000 among children with complex chronic conditions such as cerebral palsy, who accounted for just 2.8% of the tonsillectomies but 44% of the deaths. Most of the deaths were related to breathing difficulty rather than excessive bleeding.

JAMA doi:10.1001/jama.2022.8679

Persistent atrial fibrillation and MRI guided fibrosis ablation

In cases where there is left atrial fibrosis, recurrence of atrial fibrillation after conventional ablation (pulmonary vein isolation) is common. This multicentre randomised trial of 843 people with persistent AF compared conventional pulmonary vein isolation with a pulmonary vein isolation and fibrosis ablation guided by magnetic resonance imaging (MRI): it found no significant difference in recurrence of AF after three months (recurrence 46% *v* 43%).

Conventional ablation seemed to be safer in terms of a composite outcome of stroke, pulmonary vein stenosis, bleeding, heart failure, or death within one month of the ablation (2% *v* 0), although numbers were small. Further studies with larger numbers and a longer follow-up period would be valuable; with such high recurrence rates after ablation, there's clearly a problem looking for a solution here.

JAMA doi:10.1001/jama.2022.8831

Pfizer or Moderna: which vaccine is safer?

Which covid-19 vaccine is safer: BNT162b2 (Pfizer) or mRNA-1273 (Moderna)? This cohort study of 433 672 US veterans followed up for 38 weeks found a low incidence of unwanted effects and little or no difference in the first two weeks after the first dose. However, by 38 weeks, there was an excess of 10.9 ischaemic strokes, 14.8 myocardial infarctions, 11.3 other thromboembolic events, and 17.1 cases of kidney injury per 10 000 people given the Pfizer vaccine compared with the Moderna (corresponding to modest relative risk ratios of 1.17, 1.32, 1.2, and 1.16 respectively). This could be in part because Moderna prevented more cases of covid than the Pfizer jab. An astonishing 98% of participants received their second dose within the recommended interval, and the trial was well conducted. The two vaccine groups were similar, so it seems unlikely the results are explained by Pfizer being given to those at greater risk. Whether Moderna is inherently safer or just works a bit better against covid remains an open question.

JAMA Intern Med doi:10.1001/jamainternmed.2022.2109

More is less

In December 2021, Israel approved a fourth dose for everyone over 60 years old who had had their third dose more than four months earlier, to counter a covid-19 surge caused by the omicron variant. This cohort study of over 24 000 care home residents who received a fourth dose of the Pfizer vaccine, compared with a similar number who had had only three doses, found an associated fall in covid infection, hospital admissions, and death (34%, 64-67%, and 72% respectively). The estimated effectiveness of this fourth dose against the omicron variant was less than the 89% protection against infection and 92-96% against hospital admission and death attributed to the third Pfizer dose, which was given when delta was dominant. Omicron is a slippery devil, prone to immune escape; more doses of the old vaccine is the best we can do until the new vaccines in development are ready.

JAMA Intern Med doi:10.1001/jamainternmed.2022.2658

Should you avoid allergenic foods or introduce them to babies early?

If you want to reduce your child's risk of developing food allergies, should you avoid allergenic foods or introduce them early? This 2×2 cluster randomised trial from Norway and Sweden recruited women who were 18 weeks pregnant and randomised them once their babies were born to no intervention, skin intervention group (using skin emollients, bath additives, and facial cream at least four times a week from when their baby was 2 weeks old until <9 months), food intervention group (feeding peanuts, cow's milk, wheat, and egg from the age of 3 months), and a combined skin and food intervention group.

There were around 500 babies in each group, and food allergy was diagnosed in 44 children overall by the age of 3 years. Early exposure to allergenic foods (but not skin emollients) reduced the prevalence of food allergy at the age of 3 years, but preventing food allergy in one child required early exposure to allergenic foods in 63 children. On the plus side, no serious adverse events were noted.

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STATE OF THE ART REVIEW

Diagnosis and management of covid-19 in pregnancy

CPD READING
0.5 HOURS

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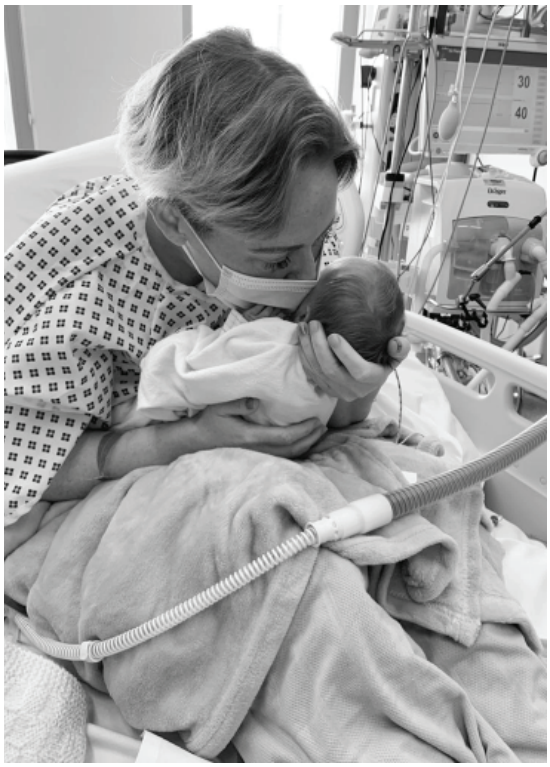
This is a summary of a State of the Art Review *Diagnosis and management of covid-19 in pregnancy*, published recently on bmj.com. The full article is available at https://www.bmj.com/content/377/bmj-2021-069739

Pregnant women appear no more or less likely to contract SARS-CoV-2 infection than the background population. However, as with other viral illnesses, the risk of developing severe disease is increased in pregnant patients compared with their non-pregnant counterparts, particularly if they contract the infection in the third trimester of pregnancy.[1 2] SARS-CoV-2 infection in pregnancy is associated with a higher risk of morbidity and mortality for both mother and fetus compared with pregnant women without infection.[1 3 4] Vaccination rates remain low among many populations of pregnant women, and ensuring that pregnant women with covid-19 receive timely and evidence based care will continue to be important for the foreseeable future.

Diagnosis and management of covid-19 in pregnancy is, for the most part, the same as in non-pregnant patients. However, important investigations such as chest radiographs and lung computed tomography (CT) are frequently withheld on account of pregnancy status, because of unsubstantiated concerns regarding fetal safety. Similarly, despite improvements allowing pregnant women to be recruited into important trials exploring effective therapies for covid-19, and a sound evidence base for treatments such as corticosteroids and IL-6 inhibitors,[6 7] pregnant women are not being offered these therapies as is routine in non-pregnant patients.[2] Special consideration is required when managing pregnant women who are severely ill with covid-19; this includes women who require respiratory support with oxygen, non-invasive ventilation, ventilation in a prone position (either awake or during invasive ventilation), intubation and ventilation, and extracorporeal membrane oxygenation. Pregnancy is not a contraindication for any of these supportive therapies, and criteria for delivering these treatments and therapeutic targets are the same as for the general population.



Facilitate contact for mother and neonate, even in the ICU setting, to support maternal-infant bonding

Epidemiology, clinical features, and risk factors for severe covid-19

Around 9% of pregnant or recently pregnant women with covid-19 develop severe infection, and 4% require admission to intensive care (odds ratio, OR, compared with non-pregnant women of reproductive age with covid-19, 2.13, 95% CI 1.53 to 2.95) and 2% go on to receive invasive ventilation (OR 2.59, 95% CI 2.28 to 2.94).[1] Additionally, pregnant women with covid-19 are at an increased risk of maternal death (OR 2.85, 95% CI 1.08 to 7.52).[2]

The World Health Organization's living systematic review shows that pregnant women are less likely to develop symptoms than their non-pregnant counterparts,[1] although the number of included women in that comparison was small. Symptoms, for those who develop them, are usually mild, and most frequently include cough (41%), fever (40%), dyspnoea (21%), and myalgia (19%).

Severe disease during pregnancy is typically a phenomenon of the late second or third trimesters. Risk factors for severe disease are similar to those in non-pregnant individuals and include age over 35, obesity, minority ethnicity, and comorbidities including pre-existing lung conditions, hypertension, and diabetes.[3 10 13 18] The increased risk associated with ethnic minority backgrounds has been shown in women who are pregnant and those who are not, with health inequalities and socioeconomic factors proposed as contributing factors.

Reference ranges of relevant investigations in non-pregnant and pregnant populations[25]				
		Pregnant		
	Non-pregnant	1st trimester	2nd trimester	3rd trimester
Observations				
Heart rate (beats/min)	60-100	63-105	68-115	65-114
Blood pressure (mm Hg)	120/80	95-138/56-87	95-136/55-86	102-144/62-96
Respiratory rate (breaths/min)	12-16	Unchanged throughout pregnancy		
Saturations (%)	>94	Unchanged throughout pregnancy		
Temperature (°C)	36.5-37.5	Unchanged throughout pregnancy		
Blood tests				
Full blood count				
Haemoglobin (g/L)	120-150	110-140		105-140
White cell count×10^9/L	4-11	6-16		
Platelets×10^9/L	150-400	150-400		
Mean corpuscular volume (fL)	80-100	80-100		
Lymphocytes×10^9/L	0.7-4.6	1.1-3.6	0.9-3.9	1-3.6
Urea and electrolytes				
Urea (mmol/L)	2.5-7.5	2.8-4.2	2.5-4.1	2.4-3.8
Creatinine (µmol/L)	65-101	52-76	44-72	55-77
Potassium (mmol/L)	3.5-5.0	3.3-4.1		
Sodium (mmol/L)	135-145	130-140		
Liver function tests				
Bilirubin (µmol/L)	0-17	4-16	3-13	3-14
Albumin (g/L)	35-46	28-37		
Aspartate aminotransferase (IU/L)	7-40	10-28	11-29	11-30
Alanine aminotransferase (IU/L)	0-40	6-32		
Gamma glutamyl transferase (IU/L)	11-50	5-37	5-43	3-41
Alkaline phosphatase (IU/L)	30-130	32-100	43-135	133-418
Inflammatory markers				
C reactive protein (mg/L)	<10	Unchanged throughout pregnancy		
Procalcitonin (ng/L)	<0.05	Unchanged throughout pregnancy		
Erythrocyte sedimentation rate (mm in 1st h)	0-20	18-48	30-70	
Other				
D dimer (µg/mL)	0.22-0.46	Not recommended for use in pregnancy*		
Troponin T (ng/L)	<14	Unchanged throughout pregnancy		
Creatine kinase (U/L)	25-200	Unchanged throughout pregnancy		
Arterial blood gas	Expect a mild compensated respiratory alkalosis in pregnancy			
Non-radiological investigations				
Peak expiratory flow rate		Unchanged in pregnancy		
Electrocardiogram		Sinus tachycardia; 15° axis deviation; commonly T wave inversion in lead III and aVF; non-specific ST changes		

*D dimer alone is unreliable as a rule-out test for pulmonary embolism in pregnancy, but will be markedly raised in hyperinflammation associated with covid-19 infection (just as in the non-pregnant population) so may be useful in this context

Clinical investigation and diagnosis

As with all medical problems in pregnancy, priority should be given to confirming a diagnosis and stabilising the woman's condition with standard investigations and therapies, and not withholding these inappropriately owing to fetal concerns. Reference ranges for relevant investigations are different in pregnancy (table).

Pregnant women with suspected covid-19 should receive appropriate imaging such as chest radiography, ventilation/perfusion scan, or computed tomography pulmonary angiography (CTPA) where indicated. Chest radiography and CTPA changes in pregnant women with covid-19 are similar to those in non-pregnant individuals, usually showing bilateral consolidation, and sometimes accompanied by pneumomediastinum.

Management

Management in pregnancy must reflect, as closely as possible, management outside pregnancy. Rapid advances have been made in developing evidence based therapies for managing covid-19, most of which are acceptable to use in pregnancy when considered on a benefit-to-risk assessment. However, data show that only around a quarter of pregnant women who would benefit from such therapies receive them, even when admitted to an intensive care unit (ICU).[2 30] When clinicians are uncertain about the use of treatments in pregnancy, they should seek urgent advice—eg, via obstetric physicians or expert obstetricians, to minimise maternal morbidity and mortality.

Pharmacological management

Corticosteroids

Dexamethasone readily crosses the placenta, and repeated doses in pregnancy have been associated with neurocognitive and neurosensory disorders in childhood.[35] Pregnant women who were recruited into the RECOVERY trial were therefore given either oral prednisolone or intravenous hydrocortisone, both of which (in contrast to dexamethasone) are non-fluorinated glucocorticoids which are therefore extensively metabolised by placental enzymes, crossing the placenta in small amounts only.[36 37] A similar pattern of conversion is seen with methylprednisolone.[38] Evidence does not suggest any harm from non-fluorinated corticosteroid use in pregnancy.[39] The most appropriate choices of corticosteroids for treatment of maternal covid-19 in pregnancy therefore include oral prednisolone 40 mg once daily or intravenous hydrocortisone 80 mg twice daily. Oral methylprednisolone 32 mg once daily or an intravenous dose of 1 mg/kg twice daily may also be considered, particularly if the patient is in an ICU setting.[8] The use of dexamethasone and betamethasone (both fluorinated glucocorticoids) should be reserved for fetal lung maturity only.[40] In such cases, on the day of administration, the corticosteroids used for maternal disease should be omitted. Outside the ICU setting, corticosteroid therapy should be given for 10 days or up until hospital discharge, whichever is sooner.[8] For patients admitted to ICU, decisions about steroid duration should be made on an individualised basis. Corticosteroids and concurrent illness

affect glucose metabolism and may cause hyperglycaemia, leading to gestational diabetes. Capillary blood glucose levels should be monitored, and sustained high glucose levels treated accordingly.[41]

Interleukin-6 receptor antagonists

In the limited data for the use of tocilizumab in pregnant patients with covid-19, administration is most frequently in the third trimester and, in all cases reported to date, the pregnancies have resulted in live births.[46] Tocilizumab is excreted in very low levels in breast milk and is not considered a contraindication to breastfeeding.[47]

Sarilumab, a similarly acting IL-6 receptor monoclonal antagonist, can be substituted if tocilizumab is unavailable.[48] Use of IL-6 receptor antagonists is reserved for those who have moderate to severe covid-19; therefore, the benefits of giving treatment are likely to outweigh any theoretical risk to the fetus. No evidence suggests that sarilumab is harmful.

Neutralising monoclonal antibodies

Data on safety for monoclonal antibodies in pregnancy are lacking; however,as the monoclonal antibodies are uniquely directed towards viral proteins, interference with fetal development is unlikely.

No data are available for the use of sotrovimab in pregnancy. However, in a cross-reactive binding assay, no off-target binding was detected using a protein array enriched for human embryo-fetal proteins. Where the expected benefit to the mother justifies this theoretical risk, it may be used in pregnancy.[58]

Antivirals

Concerns have been expressed about the safety of molnupiravir in pregnancy. Preclinical data on animal reproductive toxicity are conflicting,[59] and no human data exist regarding the safety of molnupiravir in pregnancy. Given the mechanism of action and animal data, molnupiravir is not currently recommended for use in pregnancy.

No safety data exist relating to the use of nirmatrelvir/ritonavir in human pregnancy. However, where the benefits of use during pregnancy could outweigh the risks, their use might be acceptable.

Preventing venous thromboembolism

Pregnant women and those in the postpartum period who have intercurrent illness are at increased risk of venous thromboembolism (VTE). Thus, all women presenting with covid-19 should be advised to stay hydrated, mobile, and should undergo risk assessment for VTE. All pregnant women admitted to hospital with covid-19 should be given thromboprophylaxis, unless contraindicated, during their inpatient admission. A discussion with the multidisciplinary team should take place for women in whom imminent delivery is anticipated, so that the dose of low molecular weight heparin (LMWH) can be timed appropriately to allow for regional anaesthesia, which ideally requires prophylactic dose LMWH to be withheld for 12 hours and therapeutic dose LMWH for 24 hours beforehand.

Obstetric care

Concurrent medication

Covid-19 infection may be associated with thrombocytopenia;[83] thus aspirin prescribed for pre-eclampsia prophylaxis should be withheld during the period of illness to reduce the risk of bleeding if platelets <50×10^9/L.[8]

Mode of birth and pregnancy outcomes

Most women infected with covid-19 show no evidence of respiratory compromise and should be allowed to recover from the infection and proceed as usual through the remainder of their pregnancy.[84] If a woman is admitted to hospital for covid-19 during pregnancy, regular ultrasound screening for fetal growth should be performed from 28 weeks onwards, as per the local policy.

Covid-19 status alone is not an indication for caesarean birth, and the usual indications should guide the mode of birth.

Women with symptomatic suspected or confirmed covid-19 should be advised to undergo labour and give birth in an environment that enables multidisciplinary care for the woman and her baby. They should be offered continuous electronic fetal monitoring during labour.

In cases in which the mother's condition deteriorates, individualised multidisciplinary assessment about the mode of birth should consider maternal preference and gestation.

When preterm birth is considered necessary, magnesium sulphate therapy should be administered for fetal neuroprotection up to 29+6 weeks' gestation and considered up to 33+6 weeks' gestation.[87] Administration of steroids (either dexamethasone or betamethasone) for fetal lung maturity should be considered before delivery before 34+6 weeks' gestation.[8 88]

No evidence exists of an increased risk of congenital abnormality or fetal loss before 20 weeks in women who have contracted covid-19 in pregnancy. In several recent studies of women with laboratory confirmed SARS-CoV-2 infection, however, the risk of stillbirth appears significantly increased compared with women without infection.[2 4 17 84]

No evidence suggests increased rates of neonatal morbidity in babies born at term. In addition, babies born to mothers who have tested positive for covid-19 are unlikely to contract the virus.[89]

Postpartum care

Vertical transmission, although reported, is uncommon,[89] and rates of infection are no greater when a baby is born vaginally, has skin-to-skin contact (is dried immediately after birth and laid directly on the mother's bare chest for at least an hour or until after the first feed), is breastfed, or remains in close contact with a mother who has covid-19.[92]

Covid-19 vaccination in pregnancy

Clinicians should strongly encourage pregnant women to accept vaccination against covid-19, signposting them to reliable information. Covid-19 vaccines have no biologically plausible mechanism by which to cause harm in the periconception period, throughout gestation, or during breastfeeding. A recent analysis in six European countries showed that almost all pregnant women admitted to ICUs with covid-19 in the latter half of 2021 (when vaccination was universally available) were unvaccinated.

Competing interests: See bmj.com.

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HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

This manuscript has been informally peer reviewed by a patient who was infected with SARS-CoV-2 during pregnancy and admitted to hospital under the care of three of the authors. The patient emphasised the importance of communication and collaboration of the multidisciplinary team.

UNCERTAINTIES

Who should consume high dose folic acid supplements before and during early pregnancy to prevent neural tube defects?

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CPD READING
0.5 HOURS

Neural tube defects are fatal or disabling birth defects resulting from failure of the neural tube to close approximately 21-28 days after conception.[1] Neural tube defects, which include spina bifida, anencephaly and encephalocele, are common congenital anomalies estimated to affect 18.6 per 10 000 live births worldwide; 50% of cases result in elective terminations or stillbirths.[2] Folic acid supplementation and fortification of foods are established interventions for the prevention of neural tube defects.[1]

Guidelines in many countries recommend 0.4 mg (400 µg) of folic acid per day (standard dose) for all individuals of childbearing age capable of becoming pregnant, with supplementation started 2-3 months before the intended pregnancy until the 12th week of pregnancy.[3-6] High doses (4-5 mg per day of folic acid) are commonly recommended for those with certain underlying risk factors for neural tube defects.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

A female patient of reproductive age reviewed the manuscript for accessibility to a wider patient audience. We revised the article with her suggestions to make certain statements clearer.

WHAT YOU NEED TO KNOW

- Guidelines recommend 0.4 mg of folic acid per day in the periconceptional period, and certain guidelines recommend high doses (4-5 mg/day) in women at higher risk for neural tube defects such as those with diabetes, body mass index ≥30, or taking antiepileptic medications or other folate antagonists
- For those who had a previous pregnancy affected by neural tube defect, high quality evidence from a large randomised clinical trial supports using 4 mg per day of folic acid
- We lack evidence to suggest that high doses have additional benefit in preventing neural tube defects in women with other risk factors
- Discuss with your patient their preference considering risk factors and the lack of evidence on benefits or harms of high dose folic acid to choose an appropriate dose

Uncertainty as to which high risk groups benefit from high dose folic acid use has led to variations in guidelines internationally. Most guidelines include women who had a previous pregnancy affected by a neural tube defect as candidates for high dose folic acid.[5-7] US guidelines also include those with a seizure disorder.[7] The National Institute for Health and Care Excellence (NICE) and World Health Organization (WHO) guidelines recommend high dose folic acid use for those with type 1 or type 2 diabetes, and those taking anticonvulsant treatment (see table).[5 6 8]

In 2010, the Royal College of Obstetricians and Gynaecologists advised women with a body mass index (BMI) of ≥30 to take high dose folic acid supplements.[12] Between 1991 and 1999, approximately 4.5% of women in the UK were prescribed high dose folic acid in their first trimester.[13] With about 21.3% of pregnant women in the UK having a pre-pregnancy BMI of ≥30,[14] the use of high dose folic acid supplements may have become more common in recent years.

The evidence of benefits with higher doses of folic acid relative to standard doses is limited. Aside from having had a previously affected pregnancy, the specific risk factors identifying women most likely to benefit from 5 mg of folic acid per day remain unclear.

What is the evidence of uncertainty?

No trials have compared high dose versus standard dose folic acid for neural tube defect prevention. Two systematic reviews highlight the lack of evidence regarding additional benefits of high dose folic acid.

A Cochrane review published in 2015 (five randomised controlled trials, 6708 births) found high quality evidence that periconceptional folic acid supplementation prevented neural tube defects (risk ratio 0.31 (95% confidence interval 0.17 to 0.58)) compared with no intervention. Subgroup analyses showed no additional protection with doses above 0.4 mg per day.[15] A prospective cohort study (247 831 women) in China also provided evidence supporting the use of 0.4 mg of folic acid per day for preventing neural tube defects.[21]

A systematic review published in 2017 found two observational studies that assessed the comparative effectiveness of different doses of folic acid in the US before the initiation of its food fortification programme in 1998.[22] The evidence failed to demonstrate additional benefits of doses above 0.4-1.0 mg per day.[22] Case-control studies found no additional benefits with any folic acid supplementation after the food fortification.[22] These case-

control studies have limitations, but they suggest that the low dose consumed via fortification is effective for preventing neural tube defects.

Dose in individuals with risk factors

Evidence supporting the use of 4 mg per day of folic acid among women with a previous pregnancy affected by a neural tube defect came from the Medical Research Council Vitamin Study (MRC 1991).[17] This trial (1195 women) demonstrated a 72% relative risk reduction (95% confidence interval 88% to 29%) for neural tube defect recurrence with a 4 mg per day dose of folic acid compared with a multivitamin without folic acid.[17] The choice of the 4 mg dose was pragmatic and arbitrary. It is uncertain if a lower dose would also be protective. The investigators wanted to optimise the expenses in conducting this multi-site trial; a 4 mg folic acid pill formulation was already available to treat anaemia.[3 17 25] They noted that the causal mechanisms driving the first and second occurrence of a neural tube defect are likely the same.[17] A prospective cohort study that predated the MRC 1991 trial suggested that supplementation with 0.36 mg of folic acid prevented neural tube defects among women with a previous pregnancy affected by a neural tube defect (0.6% in supplemented mothers versus 5.0% in un-supplemented mothers, risk ratio 0.11 (95% CI 0.01 to 0.85)).[26] A subsequent randomised clinical trial was too small to clearly establish a treatment effect at this lower dose.[18]

In recommending 5 mg per day of folic acid among women with type 1 or type 2 diabetes, NICE acknowledged that there was no evidence to suggest that these women would benefit from a larger dose, but women with pre-existing diabetes have higher rates of neural tube defects than women in the general population (2.4% *v* 0.57%, 4.2 times increased risk (95% CI 2.0 to 7.8)).[27 28] Similarly, the evidence cited by the Royal College of Obstetricians and Gynaecologists to recommend 5 mg per day of folic acid among women with a BMI ≥30 was that these women experience higher rates of neural tube defects (odds ratio based on combined cohort and case-control studies 1.70 (95% CI 1.34 to 2.15))[29] and lower plasma folate concentrations.[9 29] Recommending higher doses of folic acid as a solution to an elevated risk for neural tube defects in these populations assumes that their folate requirement is higher and that these neural tube defects are folate-responsive. However, there are other proposed mechanisms linking pre-existing diabetes and BMI ≥30 to an increased risk of neural tube defects that are unrelated to folate, such as poor glucose control.[30] There is a stronger biological rationale for the effectiveness of higher folic acid doses for those using antiepileptic medications or other folate antagonists, but direct evidence supporting the use of 5 mg of folic acid versus a lower dose is similarly lacking.[31]

No trials have compared high dose versus standard dose folic acid for neural tube defect prevention

Harms

There is no high quality evidence that periconceptional high dose folic acid use is associated with adverse outcomes, but possible adverse effects cannot be ruled out. Folic acid fortification results in an average consumption of 0.15 mg of folic acid per day,[32] and this dose is not known to be associated with any risks.[33] Some concerns exist regarding the long term health effects of folic acid overconsumption through supplementation, but there is no consensus.

The 2017 systematic review on folic acid supplementation for neural tube defect prevention cited only one study assessing potential harms of folic acid by dose.[22] The observational study (484 infants) reported that infants exposed to ≥0.5 mg per day of folic acid supplements in the third trimester were more likely to develop eczema than those exposed to <0.2 mg per day (41.0% eczema among exposed *v* 27.3% among unexposed, odds ratio 1.85 (95% CI 1.14 to 3.02)).[34]

The US National Toxicology Program and National Institutes of Health convened an expert panel in 2015 recommending further investigation of the effects of exposure to high doses of folic acid supplementation on the risk of cancer in exposed people and hypersensitivity related outcomes (such as allergic sensitisation and asthma) in offspring exposed during pregnancy.[35] The panel was prompted, in part, by conflicting randomised clinical trial evidence on the association of folic acid supplementation with cancer risk.[36] However, most trials were studying cardiovascular disease as their primary outcome and were not powered for the secondary cancer outcomes.[37] They were not specifically studying 4-5 mg per day use nor a pattern of use that characterises prevention of neural tube defects, which is typically for a limited duration and among a younger population.

International guidelines regarding the use of high-dose folic acid for neural tube defect prevention

Organisation*	Year	Recommendation on folic acid use
UK National Institute for Health and Care Excellence, UK[5 8]	2008	5 mg/day when planning a pregnancy or in early stages of pregnancy for personal or partner history of NTD, previous baby with NTD, personal or partner family history of NTDs, type 1 or type 2 diabetes, and when taking an antiepileptic drug
Royal College of Obstetricians and Gynaecologists, UK[9]	2010	5 mg/day for ≥1 month before conception until 12 weeks of gestation for women with BMI ≥30
American College of Obstetricians and Gynecologists, US[10]	2018	4 mg/day for previous NTD pregnancy or seizure disorder
Society of Obstetricians and Gynaecologists of Canada[11]	2015	4-5 mg/day for ≥3 months before conception until 12 weeks gestational age for personal or partner history of NTD or personal or partner with a previous pregnancy with NTD. If pregnancy does not occur after 6-8 months, change to 0.4 mg/day for 6 months 1 mg/day for medium risk subgroups (such as type 1 or 2 maternal diabetes, use of antiepileptic or folate-inhibiting medications, or having an intestinal malabsorption condition)
World Health Organization[6]	2007	5 mg/day and increased food intake of folate for those with previous NTD pregnancy, who have diabetes, or who are under anticonvulsant treatment†

NTD = neural tube defects. BMI = body mass index.

*No mandatory fortification of foods with folic acid occurred in the UK when the guidelines were issued. Mandatory fortification of foods (such as wheat and maize) with folic acid began in 1998 in the US and Canada.

†For women without these risk factors, it is advised that they take 0.4 mg/day while trying to conceive at least two months before the planned pregnancy until they are 12 weeks pregnant. The time of start and duration is not specified for those taking 5 mg/day, although it is likely to be the same.

Is ongoing research likely to provide relevant evidence?

A search of ClinicalTrials.gov with the terms "folic acid" or "high-dose folic acid" and "pregnancy" revealed that no further randomised clinical trials are planned to assess the comparative efficacy of periconceptional 4 mg per day of folic acid relative to standard doses. In terms of harms, one trial of 4 mg/day of folic acid for the prevention of pre-eclampsia follows children to the ages of 4-6 years to assess the primary outcome of autism spectrum disorder and other developmental disorders.[38]

What should we do in light of the uncertainty?

We suggest using the minimum potentially effective dose of folic acid that provides maximal risk reduction. The dose of 0.4 mg folic acid per day is sufficient to reduce neural tube defect risk for most individuals. For individuals with additional risk factors, discuss the risk of neural tube defects, guideline recommendations, and the lack of high quality evidence on the relative benefits of higher doses to allow them to make an informed decision. For those who have experienced a previous pregnancy affected by neural tube defect, taking 4 mg per day is supported by a large randomised clinical trial,[17] whereas the evidence that lower doses are effective comes from a cohort study[26] and smaller, inconclusive trials.[16 18] Among other risk factors, there is a stronger theoretical rationale for consuming higher doses when taking medications with antifolate properties, including antiepileptics. If patients choose to take 4-5 mg per day, long term exposure can be avoided by switching to a lower dose at 12 weeks of pregnancy or switching, under medical supervision, to 0.4 mg per day after 6-8 months of trying to conceive.[11] Monitoring of folate status may be warranted when making these decisions.[11] Many women at higher risk of neural tube defects are not taking any supplementation at all, and counselling them about the importance of taking a supplement before conception or in early pregnancy remains essential.

The UK government announced in September 2021 that they would introduce mandatory folic acid fortification of non-wholemeal wheat flour.[39] This measure is welcome as it will help protect those who do not take supplements during the critical period of neural tube formation. At present, supplementation is still required for the majority of the population to achieve optimal levels of protection.[1]

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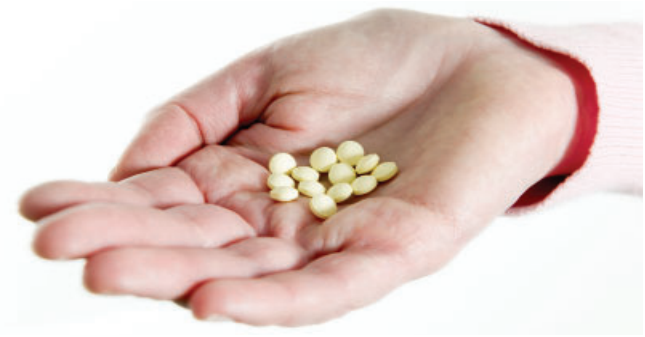
WHAT PATIENTS NEED TO KNOW



- Taking a supplement with 0.4 mg per day (standard dose) of folic acid at least 3 months before pregnancy until the 12th week of pregnancy helps prevent neural tube defects for most individuals
- Folic acid supplements should be taken in addition to consuming a folate-rich diet because diet alone does not provide maximal protection against neural tube defects
- If you have had an earlier pregnancy affected by a neural tube defect, taking 4 mg of folic acid to prevent neural tube defects is supported by evidence from a large randomised clinical trial
- There is limited evidence of any additional benefits of higher folic acid doses (4-5 mg per day)
- If you are taking medications with antifolate properties, such as certain antiepileptics, you will likely need a higher folic acid dose, but there is a lack of good evidence to show which higher dose is best
- If you have type 1 or type 2 diabetes or a body mass index (BMI) ≥30, you may be at an increased risk of having a baby with a neural tube defect, so taking folic acid supplements is especially important. However, there is no evidence to support a relative advantage of consuming a higher dose than the standard dose
- If you choose to take 4-5 mg per day of folic acid before pregnancy or in early pregnancy after a discussion with your physician, you may wish to take this dose for as short a time as needed, switching to 0.4 mg at 12 weeks or after 6-8 months of trying to conceive[11]
- Folic acid doses of 4-5 mg per day have not been associated with any side effects or harms, but there is limited evidence on this

EDUCATION INTO PRACTICE

- How will you discuss the importance of taking a 0.4 mg supplement for individuals capable of becoming pregnant or in early pregnancy?
- What risk factors would prompt you to have a discussion about high dose folic acid with an individual planning to conceive or in early pregnancy?
- How would you discuss the recommendation for high dose folic acid with these individuals?

RECOMMENDATIONS FOR FURTHER RESEARCH

Additional research is needed to clarify the definition of high risk individuals who would benefit from higher folic acid doses versus those who would not.

- High quality observational studies to assess the dose-response relation between folic acid and neural tube defect risk
- Animal and in vitro models to investigate potential biological mechanisms
- Further discussion is necessary as to whether a randomised clinical trial comparing 4 mg/day of folic acid against a standard dose would be ethical and feasible if restricted to certain high risk subgroups

MINERVA

Severe chemosis in lupus

This is the right eye of a man in his 40s who has chemosis (conjunctival oedema) of both eyes, a rare initial presentation of systemic lupus erythematosus (SLE).

He presented to the ophthalmology department with progressive blurred vision, metamorphopsia (distortion of objects), and bilateral conjunctival oedema that had developed over three months.

His visual acuity was 0.3 in his right eye and 0.4 in his left eye. Slit lamp examination reflected marked chemosis, and optical coherence tomography showed severe macular oedema.

He had no obvious systemic manifestations of SLE, but he had a primary relative with the disease and so blood tests were performed, showing high titres of antinuclear and anti-double strand DNA antibodies, low complement levels, moderate leucopenia, thrombocytopenia, and proteinuria. A diagnosis of SLE was made. He declined renal biopsy, therefore renal involvement could not be determined.

The common ocular manifestations of SLE include periocular lesions, corneal involvement, scleritis, retinopathy, and optic neuropathy. Chemosis is commonly caused by allergy but, rarely, bilateral chemosis can indicate underlying autoimmune diseases such as SLE. This unusual manifestation should prompt a clinician to consider SLE and, if appropriate, arrange further investigation and timely treatment.

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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

If you would like to write a Case Review or Spot Diagnosis for Endgames, please see our author guidelines at http://bit.ly/29HCBAL

Improving vaccine uptake

A survey of doctors in the Czech Republic finds, not surprisingly, that they have a high degree of trust in vaccines against covid-19. This is at odds with the results of a survey among members of the general public, who believed that only 50% of doctors trust the vaccines. A randomised trial showed that providing information about the true views of doctors led to a worthwhile increase in vaccine uptake (www.nature.com/articles/s41586-022-04805-y).

Vitamin D in older adults with covid

On the subject of covid-19, a randomised controlled trial from seven centres in France compared outcomes among older adults given high (400 000 IU) or standard (50 000 IU) doses of oral cholecalciferol within 72 hours of a diagnosis. It reports little or no benefit. Although survival was better in the high dose group at 14 days, the benefit wasn't sustained and by 28 days no difference was seen (*PLOS Med* doi:10.1371/journal.pmed.1003999).

Accepting uncertainty

Doctors with a high tolerance of uncertainty tended to report high levels of wellbeing and satisfaction with their chosen career, according to a survey in Massachusetts. In contrast, doctors who found it hard to deal with uncertainty were more likely to be burned out and less happy with their career choice. Female gender, working in primary care, and lack of a trusted adviser were all associated with lower tolerance of uncertainty (*J Gen Intern Med* doi:10.1007/s11606-021-06776-8).

Ultraviolet radiation and cancer risk

Although exposure to ultraviolet (UV) radiation is a major risk factor for melanoma, sunlight increases vitamin D levels, which might protect against other types of cancer. Data from three US longitudinal studies refute the notion that this is a worthwhile trade-off. Stratified by cumulative average exposure to UV radiation, increasing levels of exposure carried a greater risk not only of melanoma but also of non-cutaneous cancers (*Am J Epidemiol* doi:10.1093/aje/kwac101).

Methylcobalamin for motor neuron disease

A phase 3 trial from Japan explored the potential harms and benefits of high dose methylcobalamin (50 mg twice weekly for 16 weeks) for people with motor neuron disease. Judged by a 48 point rating scale, functional decline was slightly slower in those given the active treatment than in those who received placebo. The incidence of adverse events was similar between the two groups (*JAMA Neurol* doi:10.1001/jamaneurol.2022.0901).

Doctors who found it hard to deal with uncertainty were more likely to be burned out

Calcification in abdominal aortic aneurysms

A retrospective analysis of computed tomography data from Vienna, Austria, suggests that the presence of calcification in the vessel wall slows the progression of abdominal aortic aneurysms. Among 100 cases of patients with abdominal aortic aneurysm who were monitored by computed tomography angiography every six months, the rate of expansion of the aneurysm was inversely related to the amount of calcification in the aortic wall (*J Vasc Surg* doi:10.1016/j.jvs.2021.11.062).

Brain lesions that abolish addictive behaviour

Cigarette smokers who survive a stroke sometimes quit, not because they are advised to do so by their doctors but because the brain lesion abolishes their desire to smoke. An analysis of brain imaging in 129 such cases showed that, although the locations of the individual lesions were highly variable, they tended to be situated in regions with connections to the insula and to the cingulate and prefrontal cortices (*Nat Med* doi:10.1038/s41591-022-01834-y).

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