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Volume 88 | Issue 111 | May-Jun. 2020

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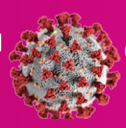

COVID-19 SPECIAL ISSUE

1 Research

Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial

BMJ 2020; 369 doi: https://doi.org/10.1136/bmj.m1849
(Published 14 May 2020)Cite this as: BMJ 2020;369:

Accepted 6 May 2020

Abstract

Objective To assess the efficacy and safety of hydroxychloroquine plus standard of care compared with standard of care alone in adults with coronavirus disease 2019 (covid-19).

Design Multicentre, open label, randomised controlled trial.

Setting 16 government designated covid-19 treatment centres in China, 11 to 29 February 2020.

Participants 150 patients admitted to hospital with laboratory confirmed covid-19 were included in the intention to treat analysis (75 patients assigned to hydroxychloroquine plus standard of care, 75 to standard of care alone).

Interventions Hydroxychloroquine administrated at a loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily (total treatment duration: two or three weeks for patients with mild to moderate or severe disease, respectively).

Main outcome measure Negative conversion of severe acute respiratory syndrome coronavirus 2 by 28 days, analysed according to the intention to treat principle. Adverse events

Dear Doctor,

We are proud to publish the next issue of the "Health Digest" written exclusively for medical professionals for their education and well-being.

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were analysed in the safety population in which hydroxychloroquine recipients were participants who received at least one dose of hydroxychloroquine and hydroxychloroquine non-recipients were those managed with standard of care alone.

Results Of 150 patients, 148 had mild to moderate disease and two had severe disease. The mean duration from symptom onset to randomisation was 16.6 (SD 10.5; range 3-41) days. A total of 109 (73%) patients (56 standard of care; 53 standard of care plus hydroxychloroquine) had negative conversion well before 28 days, and the remaining 41 (27%) patients (19 standard of care; 22 standard of care plus hydroxychloroquine) were censored as they did not reach negative conversion of virus. The probability of negative conversion by 28 days in the standard of care plus hydroxychloroquine group was 85.4% (95% confidence interval 73.8% to 93.8%), similar to that in the standard of care group (81.3%, 71.2% to 89.6%). The difference between groups was 4.1% (95% confidence interval –10.3% to 18.5%). In the safety population, adverse events were recorded in 7/80 (9%) hydroxychloroquine non-recipients and in 21/70 (30%) hydroxychloroquine recipients. The most common adverse event in the hydroxychloroquine recipients was diarrhoea, reported in 7/70 (10%) patients. Two hydroxychloroquine recipients reported serious adverse events.

Conclusions Administration of hydroxychloroquine did not result in a significantly higher probability of negative conversion than standard of care alone in patients admitted to hospital with mainly persistent mild to moderate covid-19. Adverse events were higher in hydroxychloroquine recipients than in non-recipients.

Trial registration ChiCTR2000029868.

2 Brief Report

May 1, 2020

Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19)

Question In hospitalized patients with coronavirus disease 2019 (COVID-19), what is the risk of corrected QT (QTc) prolongation when taking hydroxychloroquine with or without azithromycin?

Findings In a cohort study of 90 hospitalized patients with coronavirus disease 2019, use of hydroxychloroquine with or without azithromycin for treatment of COVID-19 was associated with frequent QTc prolongation, and those taking hydroxychloroquine and azithromycin had greater QT prolongation than those taking hydroxychloroquine alone. One patient developed torsades de pointes.

Meaning Clinicians should carefully weigh risks and benefits if considering hydroxychloroquine and azithromycin, with close monitoring of QTc and concomitant medication usage.

Abstract

Importance Administration of hydroxychloroquine with or without azithromycin for the treatment of coronavirus disease 2019 (COVID-19)–associated pneumonia carries increased risk of corrected QT (QTc) prolongation and cardiac arrhythmias.

Objective To characterize the risk and degree of QT prolongation in patients with COVID-19 in association with their use of hydroxychloroquine with or without concomitant azithromycin.

Main Outcomes and Measures Change in QT interval after receiving hydroxychloroquine with or without azithromycin; occurrence of other potential adverse drug events.

Conclusions and Relevance In this cohort study, patients who received hydroxychloroquine for the treatment of pneumonia associated with COVID-19 were at high risk of QTc prolongation, and concurrent treatment with azithromycin was associated with greater changes in QTc. Clinicians should carefully weigh risks and benefits if considering hydroxychloroquine and azithromycin, with close monitoring of QTc and concomitant medication usage.

Introduction

As of April 10, 2020, more than 500 000 cases of coronavirus disease 2019 (COVID-19) have been reported in the United States, with no US Food and Drug Administration–approved treatments to date. Against this backdrop, the use of hydroxychloroquine for COVID-19 treatment has gained traction, appearing in international and domestic therapeutic guidelines. The presumed efficacy and widespread use of hydroxychloroquine stemmed from in vitro evaluations of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and SARS-CoV-2 and a small prospective study claiming virologic clearance in 6 patients taking hydroxychloroquine with azithromycin. The combination gained further attention after coverage by the lay press; however, subsequent studies have failed to replicate these findings.

Although hydroxychloroquine and azithromycin are generally well-tolerated medications used in clinical practice, both can cause corrected QT (QTc) prolongation. With sweeping usage and perhaps insufficient consideration for comorbidities or concomitant QT-prolonging therapies, the frequency of adverse drug events (ADEs) will likely increase. Furthermore, evidence suggests that patients with underlying cardiac comorbidities are disproportionately affected by COVID-19 and the virus itself provokes myocardial injury. In this study, we aimed to characterize the risk and degree of QT prolongation in patients with COVID-19 in association with their usage of hydroxychloroquine with or without concomitant azithromycin.

administration, and comorbidities did not correlate with a QTc of 500 milliseconds or more. Forty-one patients were discharged, 4 died, and 45 remained hospitalized, with a median follow-up of 9 days. Twenty-one patients had repeated nasopharyngeal polymerase chain reaction testing after a median (IQR) of 3.0 (1.0-6.5) days after starting treatment; 0 of 8 (0%) in the hydroxychloroquine group and 1 of 13 (7.7%) in the hydroxychloroquine and azithromycin group had negative results.

Discussion

Proponents of hydroxychloroquine and chloroquine for COVID-19 treatment cite established safety in patients with autoimmune disorders, in vitro studies, and small nonrandomized clinical trials. However, the patients in these studies are clinically different from patients who were critically ill, infected with COVID-19, and receiving multiple QTc-prolonging medications with extended half-lives, which augment cardiotoxic risks.

Although hydroxychloroquine and azithromycin administration was discontinued 3 days prior to the event, the patient also had severe acute respiratory distress syndrome, bradycardia, hypothermia, propofolcoadministration, and a new cardiomyopathy, raising concerns that the risk of QTc prolongation likely persisted, given the prolonged terminal half-life of each agent

Hydroxychloroquine is structurally and mechanistically similar to the class IA antiarrhythmic quinidine, which inhibits voltage-gated sodium and potassium channels, prolonging the QT interval and increasing the risk of torsades de pointes and sudden cardiac death.6 Azithromycin also has been implicated in QTc prolongation and proarrhythmic events; its Food and Drug Administration label highlights the dose-dependent elevation in QTc when combined with chloroquine.

Within a 4-week observation period, 21 of 90 patients (23%) treated with hydroxychloroquine or hydroxychloroquine plus azithromycin had either significant QTc prolongation or ΔQTc of 60 milliseconds or greater. This underscores the American College of Cardiology's recommendation for baseline risk assessment, frequent QTc monitoring, and strict cutoffs for therapy cessation; the Infectious Diseases Society of America voices similar concerns, recommending targeted antiviral therapeutics be limited to clinical trials. Ultimately, curtailing hydroxychloroquine-associated ADEs would require a multidisciplinary effort across medicine, infectious diseases, pharmacy, cardiology, critical care, and health care quality.

Conclusions

Patients who were hospitalized and receiving hydroxychloroquine for COVID-19 frequently experienced QTc prolongation and ADEs, including a case of torsades de pointes with administration of hydroxychloroquine and azithromycin, which to our knowledge has yet to be reported elsewhere in the literature. There is a critical need for rigorous, large-scale studies and risk-benefit assessment prior to initiating COVID-19 therapeutics, with careful attention to medication interactions, cardiac manifestations, routine electrocardiograms, and electrolyte monitoring.

3 Benefits of colchicine in myocardial infarction

Experimental and clinical evidence supports the role of inflammation in atherosclerosis and its complications. Colchicine is an orally administered, potent antiinflammatory medication that is indicated for the treatment of gout and pericarditis.

METHODS

We performed a randomized, double-blind trial involving patients recruited within 30 days after a myocardial infarction. The patients were randomly assigned to receive either low-dose colchicine (0.5 mg once daily) or placebo. The primary efficacy end point was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization. The components of the primary end point and safety were also assessed.

CONCLUSIONS

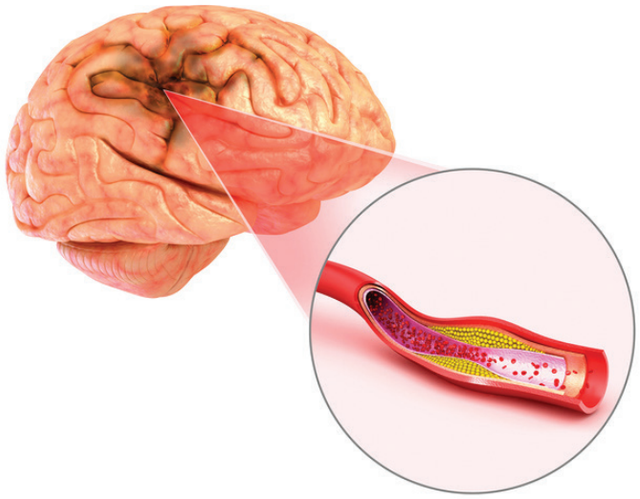
Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo.

BMJ 2020;

ABSTRACT

Stroke is the leading cause of long term disability in developed countries and one of the top causes of mortality worldwide. The key first step in stroke care is early identification of patients with stroke and triage to centers capable of delivering the appropriate treatment, as fast as possible.

Evidence based treatments such as intravenous thrombolysis and endovascular clot retrieval, which can remove the obstruction and restore blood flow to the affected areas of the brain, have been shown to improve outcomes in AIS when applied to appropriate patients, with substantial advances in these treatments occurring in the past few years.Selecting the right patients involves critical clinical assessment and brain and vascular imaging, as well as systems that provide fast but safe care, because the speed at which AIS is treated is directly related to outcome. Although other vascular causes of acute brain injury exist, such as intracerebral hemorrhage, and important management decisions must be made after the acute stroke phase, this review will focus only on the management of ischemic stroke in the hyperacute and acute phases of the disease.



4 Management of acute ischemic stroke

Pre-hospital management

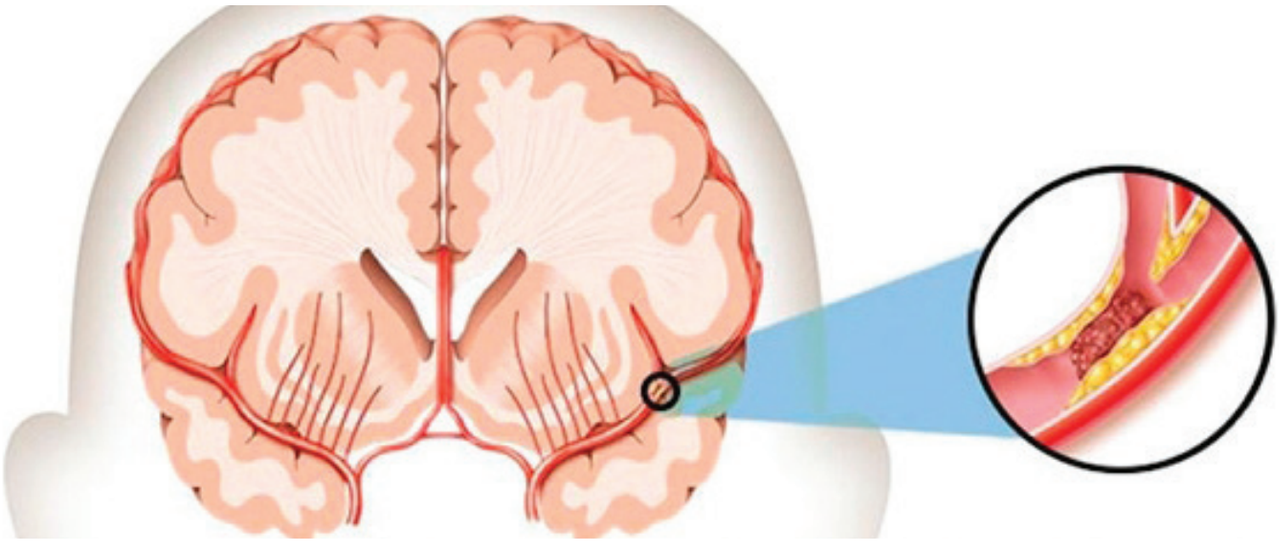
A stroke assessment system used by emergency medical services (EMS), initial management with a stroke protocol started in the field, and pre-notification of hospitals all have moderate evidence from non-randomized studies and are strongly recommended.Regional EMS systems should develop triage standards and protocols specific to stroke, using validated instruments, and an organization of hospitals with different levels of stroke care should be developed for rapid triage of the right patient to the right hospital for the right treatment, in the most efficient way

Mobile stroke units

Mobile stroke units (MSUs), have been deployed since 2010 in a few settings as a means for decreasing time to treatment for patients with stroke, by bringing the diagnostic tools and treatments to the patient. These are essentially retrofitted ambulances that include a small bore computed tomography scanner and a laboratory unit that are sent to patients with a potential stroke for evaluation and treatment with thrombolytics onsite. However, more personnel are needed to provide thrombolysis onsite, including often a neurologist, a computed tomography technician, and a critical care nurse, in addition to paramedics

Imaging in acute stroke

Acute ischemic stroke and intracerebral hemorrhage cannot



be distinguished clinically, and treatment with thrombolytics is efficacious in the first and detrimental to the second. Therefore, all patients with suspected AIS must have emergent brain imaging, and in most situations a non-contrast head computed tomography scan is sufficient for initial management. As outcomes are time dependent, brain imaging should be done as quickly as possible, ideally within 20 minutes of the patient's arrival. If it does not delay intravenous thrombolysis, non-invasive intracranial vascular imaging should be done in patients who otherwise meet criteria for endovascular clot retrieval. This can be done in combination with the initial imaging study but should not delay intravenous thrombolysis. One potential barrier to including computed tomography angiography (CTA) with the initial imaging is the concern about contrast induced nephropathy. However, evidence shows that the risk of doing CTA before obtaining a creatinine concentration in patients without known renal failure is low, and many radiology guidelines recommend that delays should not occur because of concerns about creatinine.

Perfusion imaging, using either computed tomography or magnetic resonance imaging (MRI), has been used to select patients for treatment who are outside typical time windows (4.5 hours for intravenous alteplase, 6 hours for endovascular therapy). Perfusion studies use contrast to measure the amount and timing of blood flow to certain areas of the brain, which can help to identify areas that have been irreversibly damaged or are at risk of damage if reperfusion is not achieved. Areas that have a very low blood flow have likely been irreversibly injured, whereas areas that have enough blood flow but high time to maximum of the residue function (Tmax) for the blood to reach that area are at risk but not yet irreversibly injured.

Intravenous thrombolytics

The mainstay of AIS management for the past two decades has been attempted reperfusion of ischemic tissue with intravenous thrombolysis.),

Listed contraindications on FDA drug labeling for Activase (alteplase) use for AIS

- Current intracranial hemorrhage
- Subarachnoid hemorrhage -Active internal bleeding
- Recent (within 3 months) intracranial or intraspinal surgery or serious head trauma
- Presence of intracranial conditions that may increase the risk of bleeding (eg, some neoplasms, arteriovenous malformations, or aneurysms)
- Bleeding diathesis
- Current severe uncontrolled hypertension
- AIS=acute ischemic stroke

Complications of thrombolytic therapy

When treating patients with thrombolytic therapy, providers must be able to identify and

manage the two main potential complications of treatment, intracerebral hemorrhage and angioedema. Hospitals should have protocols for reversal of coagulopathy, typically with cryoprecipitate or protein complex concentrate

Sample algorithm for acute management of ischemic stroke

Modified Treatment in Cerebral Ischemia (TICI) scale

TICI grade	Definition
Grade 0	No perfusion
Grade 1	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
Grade 2A	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory
Grade 2B	Antegrade reperfusion of more than half of the occluded target artery previously ischemic territory
Grade 2C	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with presence of visualized occlusion in one or more distal branches
Grade 3	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

Management of physiological factors

1.Blood pressure management in acute stroke

2.Patient positioning

In addition to permissive blood pressure, positioning patients fully supine (that is, with the head of the bed flat) is another strategy that has been proposed to increase cerebral perfusion in the acute stroke setting.

3.Blood sugar management

4.Oxygen management

Acute antithrombotic management for secondary prevention

Management has two main objectives when patients present with acute ischemic stroke or transient ischemic attack (TIA): to minimize disability from the acute event and decrease the likelihood of another stroke. The risk of recurrent stroke is highest soon after presentation, when presumably the factors leading to the current event are still in play (for example, ruptured atherosclerotic plaque with thrombus). Therefore, secondary stroke prevention strategies will be most successful if implemented as soon as possible.

The panel recommended starting dual antiplatelet therapy within 24 hours of onset of TIA or minor stroke symptoms and continuing for 10-21 days on the basis of the finding that this practice reduces non-fatal recurrent stroke

Conclusions

Management of AIS has undergone many changes in the past few years, with more patients receiving treatment to minimize long term disability. A critical advance has been the establishment of organized regional stroke systems of care that can quickly identify patients with stroke in the field and use decision support to get patients to the appropriate centers that can provide state of the art care for their condition. This includes doing the necessary clinical and imaging evaluation and interpretation of those results by clinicians with expertise in determining patients' eligibility for rapid administration of intravenous thrombolytic therapy and endovascular thrombectomy. The devices available for endovascular thrombectomy continue to be improved, and the appropriate procedural and subacute management of patients continue to be refined. Presentation with acute stroke is also the time to begin acute measures aimed at preventing additional strokes in this high risk population. Appropriate application of the available treatments is crucial to optimizing outcomes of patients with stroke.

5 The Effect of Sodium reduction in lowering blood pressure

The magnitude of blood pressure lowering achieved with sodium reduction showed a dose-response relation and was greater for older populations, non-white populations, and those with higher blood pressure. Short term studies underestimate the effect of sodium reduction on blood pressure.

Sodium reduction resulted in lower blood pressure among a very broad group of populations with a strong dose-response relation between the magnitude of the sodium reduction achieved and the magnitude of the fall in blood pressure. The effects of sodium reduction were more evident at higher starting blood pressure levels, older ages, and among non-white populations, but almost every population group examined achieved a reduction in blood pressure. In trials of more than two weeks' duration, the dose-response relation between sodium reduction and blood pressure fall was greater than that in trials of shorter duration

What this study adds

Evidence shows that sodium reduction lowers blood pressure in both hypertensive and non-hypertensive individuals, with greater effects in high risk subsets

The magnitude of blood pressure lowering achieved with sodium reduction showed a dose-response relation

Very short term trials could substantially underestimate the effect of sodium reduction on blood pressure.

6 Clinical Review

State of the Art Review

Pre-eclampsia: pathophysiology and clinical implications

Pre-eclampsia is a common disorder that particularly affects first pregnancies. The clinical presentation is highly variable but hypertension and proteinuria are usually seen. These systemic signs arise from soluble factors released from the placenta as a result of a response to stress of syncytiotrophoblast. There are two sub-types: early and late onset pre-eclampsia, with others almost certainly yet to be identified. Early onset pre-eclampsia arises owing to defective placentation, whilst late onset pre-eclampsia may center around interactions between normal senescence of the placenta and a maternal genetic predisposition to cardiovascular and metabolic disease. The causes, placental and maternal, vary among individuals.

Definition

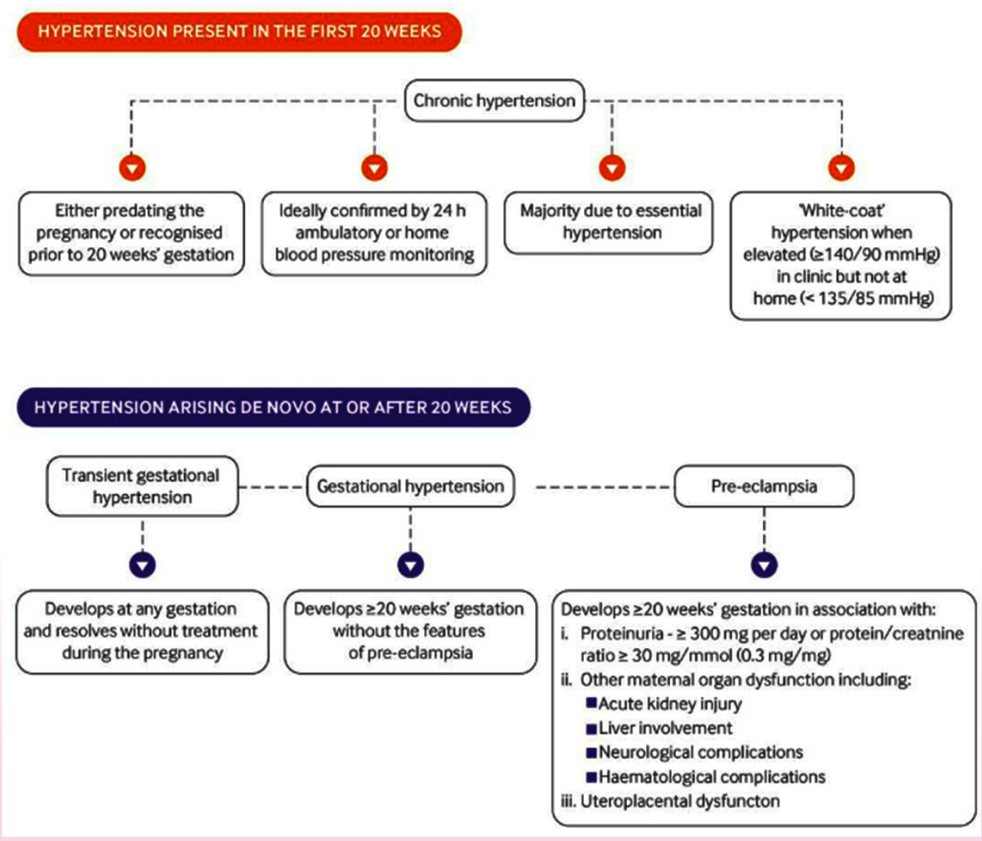
Defining pre-eclampsia is difficult,Until recently, the accepted definition of pre-eclampsia was new onset hypertension and proteinuria developing in the second half of pregnancy and resolving after delivery. Currently, the diagnosis endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) embraces new onset hypertension (systolic >140 mmHg and diastolic >90 mmHg) accompanied by one or more other features: proteinuria, other maternal organ dysfunction (including liver, kidney, neurological), or hematological involvement, and/or uteroplacental dysfunction, such as fetal growth restriction and/or abnormal Doppler ultrasound findings of uteroplacental blood flow.

Categories of hypertension in pregnancy recognised by the ISSHP8

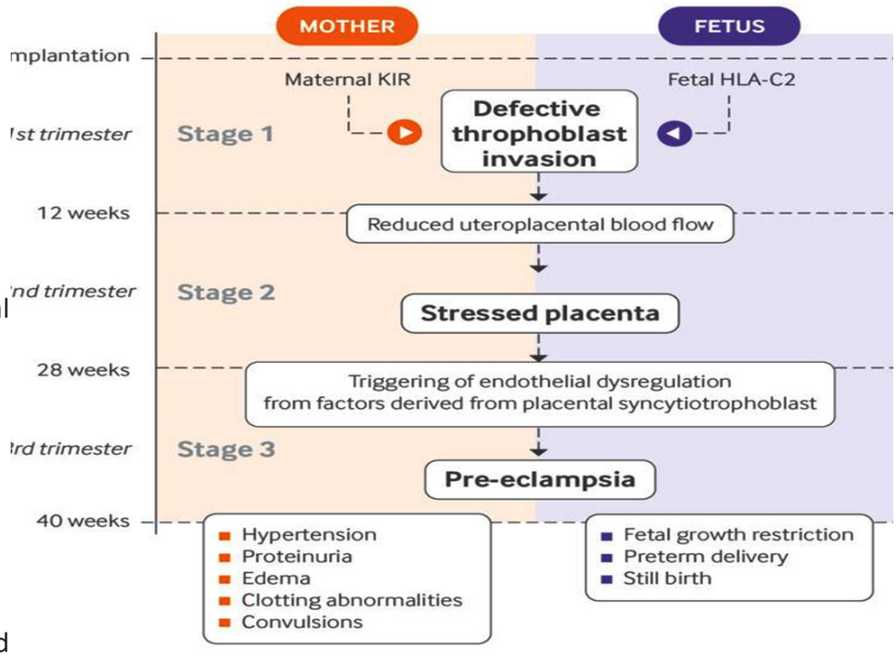
Both the ISSHP and the American College of Obstetricians and Gynaecologists recommend that the terms “severe” and “mild” pre-eclampsia should no longer be used, as all cases are potentially threatening clinically.

Risk factors for pre-eclampsia from three systematic reviews

- Chronic hypertension
- Antiphospholipid antibody syndrome
- Systemic lupus erythematosus



- Pre-gestational diabetes
- Chronic renal disease
- Multifetal pregnancy
- Pre-pregnancy BMI >30
- Previous stillbirth
- Nulliparity
- Maternal age >40
- Increased pre-pregnancy BMI
- Long inter-pregnancy interval (>5 years)
- Reduced school education
- Previous pre-eclampsia
- Assisted reproduction
- Previous intrauterine growth restriction
- Previous placental abruption



Fetal sex is increasingly recognised as an important risk feature, a predominance of female fetuses was found in those pregnancies delivering before 34 weeks

Analyses of sex differences in placental gene expression indicate that almost half are X linked and arise from escape of X inactivation. Thus, the male fetus may be more susceptible to suboptimal placentation, or less adaptable to adverse conditions. This may reflect sex differences in uteroplacentalmalperfusion. The uterine artery pulsatility index is higher, and notching of the Doppler waveform more common in women carrying a male compared with a female fetus, indicating greater vascular resistance.Hence, early loss of more severely impaired pregnancies carrying male fetuses could explain the female sex bias of early onset pre-eclampsia

The primary role of the placenta

Factors emanating from the placenta into the systemic circulation are considered to result in the maternal syndrome of pre-eclampsia.When stressed, the syncytiotrophoblast releases a complex mix of factors, including pro-inflammatory cytokines, exosomes, anti-angiogenic agents, and cell-free fetal DNA, into the maternal circulation. These disrupt maternal endothelial function resulting in a systemic inflammatory response, the clinical syndrome of pre-eclampsia.

Pathogenesis of pre-eclampsia with the subsequent effects on mother and fetus.

Screening

Pre-eclampsia is usually symptomless, making the syndrome hard to predict. Symptoms such as epigastric pain or severe headache frequently herald a terminal crisis, for example eclampsia or the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, which requires prompt termination of pregnancy. Screening of well women for the early stages of pre-eclampsia has been highly successful in limiting maternal and perinatal problems.Antenatal care is based on predictions of the chances of pre-eclampsia developing before the next screening tests are due. Pre-eclampsia is uncommon before 20 weeks, but then progressively becomes more frequent towards term and beyond. Hence, the frequency of checks is higher during the third trimester. Until recently, screening was based on timely detection of new onset hypertension and proteinuria, because they were the first features to be documented and their measurement is easy and cheap.

An increased ratio of sFlt-1/PlGF is a good marker of the placental component of pre-eclampsia, and of fetal growth restriction induced by placental malperfusion.

The ability to exclude pre-eclampsia is also important, and before 35 weeks the PlGF value can rule out the need for delivery within the next two weeks with

98% probability.When combined in the sFlt-1/PlGF ratio, this increases to a probability of more than 99% within the next week.150 As with uterine artery Doppler assessment, the ratio does not predict late onset pre-eclampsia well. Ideally, diagnosis should be made early in pregnancy, when interventions could begin before the clinical features are manifest. Combinations of demographic and clinical factors with maternal blood pressure, uterine artery Doppler measurements, and blood biomarker assessments factors have been assembled to improve predictive efficiency. A version of enhanced first trimester screening has been used in a trial of prophylactic low dose aspirin with encouraging results, identifying primarily early onset pre-eclampsia.

Therapy
Prevention

Pharmacological and behavioural efforts to prevent pre-eclampsia are at best minimally effective. Evidence that a "healthy" diet, "appropriate" weight gain and exercise,and stress reduction can reduce the riskis less than compelling;. Meta-analyses of the more than 40 000 women treated with aspirin in doses of less than 165 mg started in early pregnancy indicate a small beneficial effect to reduce the incidence of pre-eclampsia, fetal prematurity, and mortality. Current recommendations for aspirin are for women with modest to high risk. Calcium supplements of 1.5 to 2 g daily in settings with low calcium intake reduce the severity of blood pressure and adverse outcomes, and may reduce the incidence of pre-eclampsia or pre-term birth.

7

Effects of Intermittent Fasting on Health, Aging, and Disease

Reducing food availability over a lifetime (caloric restriction) has remarkable effects on aging and the life span .The health benefits of caloric restriction result from a passive reduction in the production of damaging oxygen free radicals.

metabolic disorders (obesity, insulin resistance, hypertension, or a combination of these disorders).

8 News

Ibuprofen can mask symptoms of infection and might worsen outcomes, says European drugs agency

BMJ 2020; 369 doi: https://doi.org/10.1136/bmj.m1614 (Published 22 April 2020)

The European Medicines Agency's pharmacovigilance risk assessment committee (PRAC) has recommended updating the product information for drugs containing ibuprofen and ketoprofen to warn that they can mask the symptoms of infection.

Such masking can delay treatment and worsen outcomes and has been observed in bacterial community acquired pneumonia and bacterial complications to varicella (chickenpox), the committee said after its monthly meeting on 17 April. Patients should therefore be monitored for worsening of infection when drugs containing ibuprofen and ketoprofen are used for relieving fever or pain from an infection.

9 Renin - Angiotensin - Aldosterone System Inhibitors in Patients with Covid-19

KEY POINTS RELATED TO THE INTERPLAY BETWEEN COVID-19 AND THE RENIN – ANGIOTENSIN – ALDOSTERONE SYSTEM

- ACE2, an enzyme that physiologically counters RAAS activation, is the functional receptor to SARS-CoV-2, the virus responsible for the Covid-19 pandemic
- Select preclinical studies have suggested that RAAS inhibitors may increase ACE2 expression, raising concerns regarding their safety in patients with Covid-19
- Insufficient data are available to determine whether these observations readily translate to humans, and no studies have evaluated the effects of RAAS inhibitors in Covid-19
- Clinical trials are under way to test the safety and efficacy of RAAS modulators, including recombinant human ACE2 and the ARB losartan in Covid-19
- Abrupt withdrawal of RAAS inhibitors in high-risk patients, including those who have heart failure or have had myocardial infarction, may result in clinical instability and adverse health outcomes
- Until further data are available, we think that RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, being evaluated for, or with Covid-19

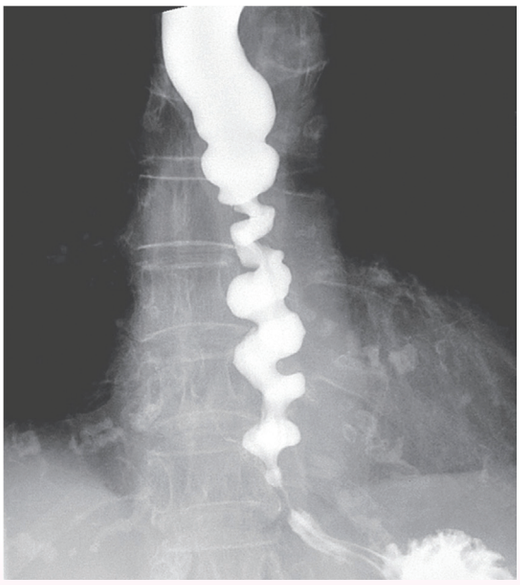


IMAGE CHALLENGE

An 83-year-old woman presented to the gastroenterology clinic with dysphagia and regurgitation that occurred with every meal associated with postprandial chest pain. For several years she had difficulty swallowing both solids and liquids. Barium esophagram is shown. What is the diagnosis?

1. *Scleroderma*
2. *Esophageal stricture*
3. *Esophageal web*
4. *Esophageal carcinoma*
5. ***Achalasia***

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