Clinical Review

Clinical Review identifies issues in the medical literature of interest to clinicians in Africa. Essential references are given at the end of each section

STI Review

Antenatal screening for sexual transmitted infections

Sexually transmitted infections (STIs) during pregnancy can lead to adverse outcomes for both the mother and newborn, including premature rupture of membranes, preterm labour, preterm delivery, chorioamnionitis, low birth weight, congenital infection, still birth, or neonatal mortality. Infection with bacterial STIs can also increase the risk of mother-to-child-transmission of human immunodeficiency virus (HIV).

Syphilis

Syphilis in pregnancy remains one of the most prevalent, but treatable, STIs. More women worldwide have syphilis than HIV infection, and focusing on untreated pregnant women, mother-to-child transmission (MCTC) of syphilis is nearly 100%, while MTCT of HIV is around 30%.[1] It is estimated that 2.7% of pregnant women in sub-Saharan Africa are infected with syphilis.[2] A model of syphilis incidence across 43 countries in sub-Saharan Africa estimates the incidence of adverse pregnancy outcomes as more than 200 000 per year, including stillbirth: 88 376; neonatal death: 34 959; low birth weight: 22 483; and congenital syphilis: 60 084.[3] In 2007, the World Health Organization (WHO) launched a global initiative to eliminate mother-to-child transmission (MTCT) of syphilis. According to the health systems model used to monitor progress, between 2008 and 2012, maternal syphilis declined by 38% and congenital syphilis by 39%.[4] Much of the decline was seen in southeast Asia, with little change in Africa, the region with the largest congenital syphilis burden. However, a ten-year cross-sectional study of syphilis and HIV in pregnant women in Rwanda found the overall prevalence of syphilis decreased from 3.8% in 2002 to 2.0% in 2011.[5] Syphilis in HIV-infected women increased from 6.0% to 10.8%, but decreased from 3.7% to 1.7% in HIV-negative women. Positive HIV status and young age were risk factors for syphilis infection, while HIV-syphilis coinfection was associated with a lower level of education and urban residence.

There is emphasis now on dual elimination of mother-to-child transmission of HIV and syphilis (EMTCT).[6] According to the processes and criteria set by WHO, UNAIDS, UNICEF, and UNFPA to validate EMTCT, three countries have achieved EMTCT: Cuba, Thailand, and Belarus. Moldova has been validated for EMTCT of syphilis, and Armenia for HIV. These successes are at least in part a result of the process criteria required for validation, which include: 95% of pregnant women to receive antenatal care; 95% of pregnant women to receive HIV and syphilis testing in pregnancy; and 95% of pregnant women diagnosed with HIV or syphilis to receive treatment. Countries with high- and low-maternal HIV and syphilis prevalence face different challenges. Even when antenatal care screening for HIV and syphilis are provided, protocols may need to change as infection levels change. A study in Tanzania, where the protocol is to screen once during pregnancy for HIV and syphilis infection, found that some women seroconvert during pregnancy.[7] Of 331 pregnant women who screened negative for syphilis during antenatal care, 2.7% (nine) were seropositive at delivery, and of the 391 women who screened negative for HIV during antenatal care, 2% (eight) were HIV-positive at delivery. Rescreening for syphilis and HIV during pregnancy and at delivery can identify women and infants at risk and provide an opportunity for treatment.

Penicillin

The good news is that one injection of 2.4 IU benzathine penicillin G intramuscularly is all that is needed to cure early stage syphilis in a pregnant woman.[8] Those with later or unknown stage infection should receive three injections, each one week apart. Unfortunately, there are reports of penicillin shortages in many countries, including more developed countries, like the United States, where syphilis rates are increasing.[9] One of the reasons for the shortage is the lack of profitability for pharmaceutical companies manufacturing the drug. There are only four pharmaceutical companies that manufacture the base ingredient for benzathine penicillin G, and three of them are in China. Another reason for the shortage is the lack of data on the exact demand for injectable penicillin. A recent study estimates this need for treating pregnant women with syphilis in 30 high-morbidity countries, 17 of which are in Africa.[10] Assuming treatment of 95% of those screened for syphilis requires treatment for 497 142 women in the 17 African countries (an increase of 252 911—more than double—the current antenatal screening), and 244 231 doses of weight-based benzathine penicillin would be needed to treat the live-born infants of those mothers who test positive. Assuring availability and treatment, this could prevent 252 518 adverse birth outcomes in the African countries reviewed.

Other STIs

Practices for antenatal screening for curable STIs, including *Treponema pallidum* (syphilis), *Neisseria gonorrhoeae* (gonorrhoea), *Chlamydia trachomatis* (chlamydia), and *Trichomonas vaginalis* (trichomonas) vary greatly. The WHO has guidelines for screening and treatment of syphilis and HIV in pregnancy, but recommends using the syndromic approach for chlamydia and gonorrhoea, both of which are often asymptomatic.[11] There is limited data on the prevalence of STIs in pregnant women in low- and middle-income countries, but a recent systematic review of 75 studies worldwide found Southern Africa has the highest prevalence of

curable STIs among pregnant women.[12] Trichomonas infection was most prevalent, with an adjusted mean prevalence of 24.6% in three studies. Second was syphilis, with adjusted mean prevalence of 6.5% in eight studies, and, third was gonorrhoea, with adjusted mean prevalence of 4.6% in three studies, and 4.4% in three other studies. The review found studies in West and Eastern Africa also showed high prevalence of STIs.

A study of 1480 pregnant women, who were HIV-infected or at high risk of HIV infection, in KwaZulu Natal, South Africa found 32.3% tested positive for gonorrhoea, chlamydia or trichomonas, and 19.2% tested positive 14 weeks postpartum.[13] The high proportion who tested positive postpartum indicates many women continue to have unprotected sexual intercourse. More than 50% of the women with an STI during pregnancy and more than 80% with an STI post-delivery were asymptomatic. A study of 426 pregnant women in Khartoum, Sudan similarly found STI infection prevalence was high (trichomonas, 7.8%; chlamydia, 4.9%, gonorrhoea, 0.0%; syphilis, 5%), and the positive predictive value (likelihood that those with a positive test actually have the infection) of syndromic diagnosis was only 14.1%.[14] A study of rural pregnant women in Kilifi, Kenya found curable STI infections in 20.8% of the women.[15] A large-scale screening of 1862 pregnant women in Ile-Ife, Nigeria using a rapid test for chlamydia found 13.2% (222) were infected.[16]

Point-of-care testing

These results all highlight the need for point-of-care (POC) STI tests that can be used to screen pregnant women during antenatal care visits. There are several rapid POC tests available for syphilis, which can simplify testing and treatment.[17] A study in Tanzania found that introducing rapid syphilis testing (RST) at antenatal clinics significantly improved uptake of syphilis screening.[18] Three months after the introduction of RST, the number of women who attended antenatal clinics doubled, from 3561 to 7954, and the number of women tested for syphilis increased significantly, from 17.9% (636/3561) to 100% (7954/7954, P<0.01). RST also increased treatment of infected women, from 46.3% (50/108) to 94.8% (862/909, P<0.01). The provision of same day testing and treatment encouraged women to attend the antenatal clinics, and saved them time and extra cost required to return later for test results. The simplified RST technology also permitted lower level health workers to perform the screening with minimal supervision.

Dual HIV/syphilis rapid tests have also been developed.[19,20] These use finger stick whole blood samples, but simplify testing by requiring fewer blood draws and provide results in one test. Since treponemal (TP) antibodies persist in the blood, confirmatory tests may be needed to determine active syphilis infection. There are new combination TP/non-TP rapid tests that can be used to diagnose syphilis at the point of care where traditional laboratory-based testing is not available. Where tests confirming active syphilis infection are not available, and depending on syphilis prevalence in the population, it is preferred to treat all pregnant women who test positive in order to prevent MTCT.[17]

While there are rapid POC tests available for *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), and *Trichomonas vaginalis* (TV), there is a wide range of sensitivities across different tests, which leads to missed infections and continued transmission. There is currently one nucleic acid amplification test (NAAT) test, the GeneXpert® system, available for POC testing of CT, NG, CT/NG combined, HPV, and TV, which shows very good results.[19] A study in Gaborone, Botswana using this test on self-collected vaginal swabs found high acceptability among pregnant women and mostly immediate treatment.[21] Of the 200 participants, 72% received results the same day. Fifteen percent (15%) (30/200) tested positive for an STI, all received treatment, with 80% (24) receiving treatment the same day. As always, the high cost of these POC tests continue to be a barrier to their widespread use in resource-limited settings.

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Medicine Review

The 'nocebo' effect

All doctors know of the placebo effect, but who has heard of the 'nocebo' effect? The term was introduced some time ago (1961)[1] to denote the opposite of placebo, but has been brought back into use recently following a recent trial of statin side effects. Statins are powerful reducers of serum cholesterol levels, with evidence-based reductions in morbidity and mortality risk, particularly in those with established vascular disease (coronary artery, cerebrovascular or peripheral vascular disease). However, a major obstacle to their uptake in many western countries has been the potential side effects of myositis or myalgia. In Britain, newspapers have not infrequently published 'scare stories' about muscle side effects, adversely affecting patients' willingness to take these drugs.

However, a recent study published in *The Lancet* compares the rates of muscle-related side effects in two studies—one a blinded trial comparing atorvastatin 10 mg daily with placebo, followed by a similar unblinded study.[2] In the first trial, where the patients did not know which drug they were taking, muscle side-effects occurred in 2.03% per annum in those on atorvastatin and 2.00% per annum in those on placebo (no significant difference). However, in the unblinded phase, where patients knew whether they were taking the statin or not, muscle side effects occurred in 1.26% per annum in the atorvastatin group compared with 1.00% per annum in those on placebo (p=0.006).

In an accompanying editorial,[3] it is suggested that 'the nocebo effect reflects changes in human psychobiology involving the brain, body and behaviour rather than drug toxicity', and that in the case of statins 'negative press reports', and 'poor understanding of…. statin-associated side effects' may be important underlying factors.

In praise of worms?

A fascinating recent article in the *Transactions of Tropical Medicine and Hygiene*, reviews the complex, and sometimes beneficial, relationship between parasitic helminths and their human hosts.[4] The writers are a collaborative group from Uganda and London, who challenge current concepts of mass anthelmintic treatment.

It has been known for some time that human worm infections have subtle but important effects on their host's immune system. Perhaps best known is a potential protective effect on the development of allergy-based diseases. Thus, hookworm infections can reduce the risk of asthma development by up to 50%, and *Trichuris* and *Ascaris* infections can reduce the risk of eczema. The effects are particularly seen with infections in early childhood, and even in pregnant women.

Worm infections can also alter responses to vaccine administration. The effect is a negative one, such that if a vaccine is given to a subject with an active and untreated worm infection, the immune response to the vaccine is impaired, with subsequent reduced preventive effects. It has been suggested that the poor observed efficacy of BCG vaccine in Africa may be due to widespread worm infections.

Finally, there is also evidence of helminth infections protecting against type 2 diabetes. This is supported by both animal and human research. Thus, patients in China with schistosomiasis had lower fasting plasma glucose levels than non-infected controls. In Australia, aboriginal adults with previous *Strongyloides stercoralis* infections had a reduced risk of type 2 diabetes. How this interaction between worms and human metabolism operates is not known.

In their conclusions, the authors ask the question as to whether mass deworming is advisable, pointing out that there is a subtle symbiosis between humans and worms, which should at least be considered in the debate over the effectiveness and advisability of mass drug administration (MDA) programmes in Africa.

Drug stores in Africa

The ideal system for provision of drugs in Africa is via hospital pharmacy departments, or from supplies held at primary health clinics. However, there is a large 'over-the-counter' market, particularly in West Africa. These establishments are often known as 'drug stores' or 'drug shops', and a recent article in *The Lancet* has drawn attention to their advantages and disadvantages.[5]

Drug stores are not run by qualified pharmacists, but ideally the proprietors should have some sort of formal health training. In reality, many do not, and despite this regularly dispense a variety of analgesics, antibiotics, anti-malarials and family-planning products. The degree of utilisation of this peripheral form of healthcare varies widely around Africa—in some countries it can be 80% or more. In parts of southern Nigeria, there are more drug shops than standard public and private hospitals and clinics, providing first point-of-care for up to 50% of under-five childhood illnesses and at least 35% of adult malaria cases.

The potential for mis-treatment and under-treatment is obvious; but nevertheless these facilities can be an important part of primary health care in Africa if properly staffed and organised. Initiatives in Nigeria have led to a major increase in training of drug shop employees. This is to be welcomed—this system of care is popular with the public and is not going to go away. Drug shops need to be integrated into national health systems. Properly regulated they can provide an important primary care service.

Antimalarial drug problems

Most malaria in Africa is due to *Plasmodium falciparum*

and artemisinin combination therapy has become first-line therapy. In south-east Asia there have been reports of treatment failures due to substandard or counterfeit preparations, particularly in 'shop-bought' preparations. A recent study from Nigeria suggests that this problem may be emerging in Africa.[6]

The researchers chemically analysed 20 different brands of artesunate-containing antimalarials and 10 brands of artemether-lumefantrine, obtained from different sources in south-western Nigeria. Of the 10 artemether-lumefantrine combinations, two contained inadequate lumefantrine (88% and 52%) and four others failed other pharmacological standards. The 20 artesunate-containing preparations included five (25%) which did not reach standard assay requirements (containing less than 90% of the drug amount stated on the label).

The authors point out that this is likely to be a growing problem, and as well as leading to treatment failures, will be likely to reduce public confidence in these vital drugs.

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Paediatrics Review

Newborn resuscitation and early respiratory support

In high-income countries (HIC) now much of the thrust is finding optimal ways to improve the management of resuscitation and respiratory care, particularly for RDS, in infants < 32 weeks gestation (very preterm infants) through multicentre randomised controlled trials (RCT). Whereas in low- and middle-income countries (LMIC), especially in low-resource settings, the main emphasis is in establishing the basic management of newborn care universally.[1] In HIC ways are being adapted to reduce invasive practices, in particular by avoiding routine prolonged intubation and mechanical ventilation (MV) of very low birth weight (VLBW) infants and thus the risk and severity of bronchopulmonary dysplasia (BPD). BPD affects up to 50% of infants born less than 28 weeks gestation who receive standard respiratory care for RDS.[2]

Resuscitation

In general, around 3% of newborns require positive pressure ventilation at birth, fewer infants need endotracheal intubation, and cardiac compression and/or adrenaline are required in < 1%.[3] In LMIC these proportions will be higher.

Where possible SpO_2 should be measured by pulse oximetry using the hand/wrist (preductal O_2 levels). Clinical assessment of degrees of oxygenation using skin colour correlate poorly with SpO_2.[3] Ventilation will depend not only on available equipment but also the type of gas supply, i.e. air, oxygen or a mixture which will depend on the method of supply, e.g. central O_2 and gas supply, portable oxygen cylinders or oxygen concentrators. The simplest method is self-inflating bag-valve mask device with air only especially for term and near–term infants.[4] Airways obstruction occurs in 25–75% of preterm infants when ventilated by mask which impedes effective delivery of O_2.[3] Thus, most very preterm infants will require nasal continuous positive airway pressure (CPAP) to maintain airway distention. Both mortality and BPD are reduced in infants < 32 weeks who are treated with nasal CPAP in the delivery room rather than being intubated.[5] For CPAP a T-piece device is the simplest method.

Very preterm infants are at high risk of hyperoxia-induced pulmonary injury because mechanisms to protect against oxygen-free radicals are underdeveloped. When infants < 28 weeks (and also those born at term) are exposed to high O_2 concentration in the delivery room oxidative stress markers can be detected which persist for up to a week.[3] A systematic review and meta-analysis has shown that resuscitation of infants with air reduced mortality compared to infants resuscitated with 100% O_2.[6] Infants born at term or near term should be initially resuscitated with air. Preterm infants should no longer be initially resuscitated with high O_2 concentrations (65–100%) but with around 30%.[3]

The risk of hypothermia both during resuscitation of infants at birth and transfer of infants to an incubator is well recognised in LMICs. It is usually due to failure to keep infants warm but may also reflect the severity of their condition. For infants < 1500 g every one °C decrease in body temperature in the Neonatal Intensive Care Unit (NICU) is associated with an increase in mortality risk of 28%.[7] Skin-to-skin care is very effective when possible, other methods include plastic wraps or bags, plastic caps, and exothermic mattresses (EMS), but stockinet caps do not seem to be effective.[8] The efficacy depends on the particular weight of the infant. However, hyperthermia can be a problem when infants are in both plastic bags and on EMS.[9]

Tracheal suction for infants born through meconium-stained amniotic fluid, especially before the first breath, can reduce the amount of meconium entering the lungs. However, RCTs of suctioning vigorous infants have shown no benefit and thus the procedures is no longer advised.[10] Two recent studies in non-vigorous infants have also not demonstrated a benefit of routine suctioning.[11,12] Larger studies are required to confirm that the practice is not necessary in this group of infants.

Delayed umbilical cord clamping (after one minute or when the cord stops pulsating) has advantages over early cord clamping (< 60 seconds). Infants have increased haemoglobin at 24–48 hours and increased iron stores at 3–6 months which is particularly important if there is maternal anaemia.[13] The one disadvantage is hyperbilirubinaemia which is of particular concern in LMIC if routine phototherapy is not readily available and in regions where G6PD is

prevalent. Cord milking is where the cord is clamped at up to 40 cm from the umbilicus and massaged. It has similar benefits but is not superior to cord clamping.[14] Delayed cord clamping in 24–36 week gestation infants may be associated with less requirement for blood transfusion, less intraventicular haemorrhage and lower risk of necrotising enterocolitis.[15] This has to be balanced with the need for immediate resuscitation in many VLBW infants. Further studies are required especially on the longer term outcomes.[3]

Hypoxic-ischaemic encephalopathy (H-IE) resulting from moderate to severe peripartum asphyxia complicates one to three infants per 1000 at-term live births in HIC and 20/1000 in LIMC. Over a quarter of affected infants develop cerebral palsy and cognitive impairment.[3] Moderate hypothermia (within six hours of birth) for 72 hour, usually whole body, or in selective cases just head cooling, is undertaken in both inborn and outborn infants. Continuous core (rectal or oesophageal) temperature (33–34°C) monitoring is required to prevent over cooling.[3] A systematic review of 11 RCTs concluded that hypothermia reduces death or major disability at 18 months by about 25% which is sustained until school age.[1,16] Presently hypothermia therapy for H-IE should only be considered in NICUs with multidisciplinary expertise, equipment and protocols[3] which excludes its use in low–resource and many middle-income countries.

Respiratory care

In LMIC as more sophisticated facilities for neonatal care become available resulting in survival of more VLBW infants there is an increased risk of retinopathy of prematurity and BPD. Pulse oximetry for all LBW infants becomes essential, however, it is limited in detecting hyperoxia. A number of RCTs have examined using O_2 saturation targets of 85–89% or 91–95% for infants < 28 weeks. A meta-analysis of five trials found a higher risk of death in the lower saturation target O_2 group.[3] The American Academy of Pediatrics guidelines now recommend a target of 85–95% whereas European guidelines recommend a target of 90–95% saturation.[3]

Paradoxically, as surfactant becomes more available for preterm infants in some LMIC, in HIC there is a move away from routine use. A meta-analysis of 11 studies concluded that with the practice of routine administration of corticosteroids for preterm labour and use of more non-invasive respiratory support such as CPAP there was no advantage of routine over selective use of surfactant; the latter is associated with a lower mortality and risk of developing BPD.[17] Nonetheless, around 50% of extremely preterm infants will subsequently require intubation and administration of surfactant. Multiple doses of surfactant and animal-derived products especially porcine-derived are optimal.[2] Trials of new generation synthetic surfactants containing phospholipids and surfactant-protein analogues are in progress.[2]

In HIC, where possible, CPAP is undertaken using MV via the nose (rather by intubation) and when necessary it is combined with nasal intermittent positive pressure ventilation. For many NICUs in LMIC, CPAP is undertaken with a simple bubble CPAP (BCPAP) apparatus. A systematic review of use of BCPAP for RDS in infants in LMIC was undertaken.[18] In three studies, the initial use of BCPAP followed by MV, if required, reduced the requirement of MV by 30–50%. Three other trials compared BCPAP with CPAP administered by MV and found that mortality and complication rates were similar and there was a lower failure rate in the BCPAP groups.

In some LMIC neonatal respiratory care is slowly merging towards practices in HIC, as the latter move away from routine intubation, delivery of surfactant and MV. Differences remain owing to availability of expensive equipment, particularly more and more sophisticated ventilators, and the luxury of relatively large numbers of highly trained neonatologists and nurse practitioners.

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