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Medical complications of opioid use disorder in pregnancy

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ABSTRACT

Women with opioid use disorder are at increased risk of other medical complications of pregnancy. Providing care for such complex patients requires the ability to 1) acknowledge addiction as a chronic disease, 2) incorporate the altered physiology of pregnancy, and 3) devise a treatment plan that can effectively manage acute conditions. A basic tenet of care is rooted in experience, rather than evidence, but includes stabilization of opiate use disorder (OUD) as a primary goal of management of other medical complications of pregnancy. Proceeding with treatment for other medical conditions will be suboptimal without stabilization of the underlying chronic disease process.

This chapter outlines some associated medical complications of OUD both in general and some of which are unique to pregnancy: infectious diseases, soft tissue infections, endocarditis, cholestasis of pregnancy, and overdose.

Introduction

The management of medical complications of opiate use disorder (OUD) while a woman is pregnant can be a daunting task to the clinician. Often physicians outside of obstetrics and gynecology are hesitant to provide optimal care to pregnant women with any medical complications. When pregnant women have the chronic disease of addiction, the task of finding care can become overwhelming to the patient and providing care can be overwhelming to the physician.

In treating women with opioid use disorder it is imperative to both stabilize the chronic disease process of addiction and to treat other medical diagnoses. Without stabilization of opioid use disorder, treatment of other conditions will be suboptimal. We acknowledge the obstacles which impede our ability to execute such a plan, but suffice to say that the management of underlying addiction will allow improved management of both the pregnancy and the medical complications encountered.

Infectious diseases

People who inject drugs (PWID) are at risk for infectious diseases, such as HIV and viral hepatitis (A, B, and C). Injection drug use places one at risk for HIV, HBV, and HCV both from the direct risks of sharing needles or other drug preparation equipment, but also from engaging in high risk sexual behaviors associated with drug use. This rationale similarly applies to HAV, which occurs via fecal-oral transmission, as HAV could be spread parenterally via contaminated needles, as well as high risk sexual behaviors.[1] It is estimated that

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9–12 % of new HIV cases, 50% new HCV cases, and 2% of new HAV cases are associated with illicit drug use.[2–5] HBV remains a risk in PWID, though vaccination programs have decreased the incidence of new infections in the western world.

The efficiency of viral spread based upon needle stick is best modeled in the exposed healthcare worker. Based upon occupational needlesticks, a single exposure carries a 6–30% chance of transmission of HBV, 1.8% chance of transmission of HCV, and 0.3% chance of transmission of HIV.[6] Though this may seem reassuring, it is postulated that the population risks are multifold when a person injects drugs infected with HCV. It is thought that each person who injects drugs infected with HCV is likely to infect 20 more people.[7]

Depending upon populations and chronology of PWID studied, the seroprevalence rates of viral infections in PWID varies: HCV has a 60–80% seroprevalence rate in this population, HIV 20%, HBV 5–10% and HAV 19–20%.[8,9] The approach to HIV and HBV in the pregnant woman with OUD is not controversial. We have well established systems of care for screening, diagnosis, and treatment for HIV and HBV in pregnancy, which apply as well to the pregnant woman with OUD. Screening for HIV and HBV identifies those women eligible for intervention. If diagnosed with HIV, highly active antiretroviral therapy (HAART) is safe in pregnancy, and has all but eliminated the possibility of mother to child transmission (MTCT) of the disease when appropriately employed.[10,11] Clinicians have demonstrated an understanding of the gravity of the diagnosis of HIV, and their efforts are supported by federal programs, such that long-term care of the mother/infant dyad is not scarce.[12]

In a similar fashion, universal screening for hepatitis B has identified the population at risk for MTCT. HBV is highly pathogenic and infectious (10–20% chance of perinatal infection for HepBSAg positive women, and >90% chance if HepBSAg + HepBeAg positive). Postnatal prophylaxis, in the form of hepatitis B immunoglobulin (HBIG) and HBV vaccination is effective for prevention Hepatitis B MTCT, but will not be beneficial to those infants infected *in utero*.[13] Of late, in women with significant viremia, antiviral treatment has been suggested as a safe intervention to further decrease MTCT. Antiviral treatment is particularly effective for prevention of *in utero* infection.[14,15]

Such consensus has not been established for HCV. When infected with HCV, the MTCT rate is 5–8%. Risk factors for transmission include maternal viremia (though a threshold for increased risk of transmission has not been established), prolonged rupture of membranes, blood mixing at time of delivery, and invasive monitoring or operative deliveries. Should a patient be HCV antibody positive, with absence of viremia, her risk of MTCT approaches zero. This situation is most likely to occur when one has been exposed to and subsequently cleared the virus. To date, there is no obstetric intervention recommended to prevent MTCT.[16] Recently, the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) have called for universal screening of pregnant women for HCV.[17] The rationale is that with universal screening, we may be able to more adequately identify the pediatric population at risk and align pregnant women to receive appropriate direct acting antiviral treatment postpartum. At present, antiviral treatment for hepatitis C is not available for use in pregnancy, and loss to follow up remains a significant issue for the potential initiation of treatment for both women and their babies. The American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM) have not endorsed universal screening for these reasons.[13,16]

HAV deserves mention, because it represents a different degree of risk in the PWID population than the general population. In the general population, this disease presents little risk. However, given the high background risk of chronic liver disease in PWID, HAV can be devastating. HAV causes fulminant hepatic failure in <0.01% of the general population, but 6.4% in PWID. Additionally, acute HAV in patients with chronic liver disease can result in mortality several times the rate of mortality in the general population.[1]

This discourse is not intended to be a comprehensive review of the viral infections that can impact the pregnant woman with OUD; however, it is intended to point out the contemporary controversy regarding HCV screening, and to emphasize the need for primary prevention of these infections. Medication assisted treatment (MAT) in and of itself has been shown to decrease the incidence of viral infections in PWID.[18,19] Needle exchange programs and vaccine programs for HBV and HAV are essential to the care of the pregnant woman with OUD as a means of harm reduction.[20] Though needle exchange programs require the cooperation of public health departments and require an appropriate system of care, vaccine programs can be operationalized into prenatal care for this unique subset of women. *With close evaluation of susceptibility to HBV and HAV added to standard prenatal laboratory evaluations*, such vaccines can be guided and encouraged by the obstetrician-gynecologist. Vaccines for hepatitis A and B do not contain live virus, and can be administered safely in pregnancy. In addition, there is some evidence that demonstrates that accelerated vaccine administration (0, 1, 2 months versus 0, 1, 6 months) increases the likelihood of completion of the hepatitis B series in PWID.[21]

Cholestasis of pregnancy

Cholestasis of pregnancy is not a disease unique to pregnant women with OUD, but there is an association of between cholestasis of pregnancy and chronic liver diseases such as HCV and non-alcoholic liver cirrhosis.[22] An average of 0.2–2% of pregnancies overall are affected by cholestasis. HCV represents a significant risk for developing cholestasis. In a meta-analysis, the pooled OR of ICP in HCV-infected pregnant women compared to non-HCV pregnant women was 20.40 (95% CI, 9.39–44.33, I^2 = 55%). Also interesting, the pooled OR of later HCV infection among ICP patients compared to non-ICP patients was 4.08 (95% CI, 3.13–5.31, I^2 = 0%). This suggests that in patients that are not identified to have HCV, should they develop cholestasis of pregnancy, HCV screening is warranted.[23]

Cholestasis of pregnancy is diagnosed by pathognomonic itching of the palms and soles, elevated bile acids, and is associated with elevated hepatic function testing. This is a significant disease process because it is associated with adverse

pregnancy outcomes, such that delivery is recommended to occur by 37 weeks to avoid stillbirth. The exact etiology of stillbirth is not completely understood, and some have suggested that elevated bile acids in the fetal compartment are cardiotoxic resulting in fatal arrhythmia, versus vasospasm of the placental chorionic surface vessels. Thus, indicated delivery at a time when it is reasonable to assume fetal maturity is the current standard. Increased morbidity is associated with higher bile acid levels, therefore the management of cholestasis is rooted in 2 main goals: reducing symptoms and reducing the risk of perinatal morbidity and mortality. The latter assertion is based upon the presumption that lowering bile acids will have improved prognosis for the fetus, but this has not been universally established. Antihistamines have been recommended to address pruritis. Ursodiol and cholestyramine are utilized to alter the physiologic milieu and decrease circulating bile acids, which also leads to less itching. Dexamethasone has been evaluated as a possible intervention, but did not perform favorably with regard to itching or modification of bile acids. As cholestyramine has been associated with significant side effects, ursodiol has emerged as the recommended first-line treatment for cholestasis.[24]

Soft tissue infections

Intravenous and subcutaneous injection of opioids can precipitate soft tissue infections such as cellulitis and abscesses. Cellulitis can occur from bacterial entry through skin barrier breakdown and direct exposure of contaminated needles and drug paraphernalia which causes superficial skin inflammation. Other risk factors include inflammatory skin disorders (eczema, radiation), obesity, immunosuppression (HIV, diabetes), and preexisting skin infections (fungal, bacterial, viral).[25] Abscesses are characterized by purulent fluid collections in the dermis or subcutaneous spaces. The most common pathogen for cellulitis is beta-hemolytic streptococcus (Group A *Streptococcus* and Streptococcus *pyogenes*) followed by *S. aureus* and gram negative aerobic bacilli.[26] With regard to abscesses, 75% of cases are caused by *S. aureus*. Sterile abscesses are also common with injected drugs.[27] If the material is not fully absorbed, remnants accumulate at the site of injection and cause local irritation that turns into a solid lesion as it scars.[28]

Diagnosis of soft tissue infections is typically made clinically. Cellulitis is characterized by skin erythema, edema, and warmth, with or without purulence. The differential diagnosis includes herpes zoster, septic arthritis, septic bursitis, osteomyelitis, contact dermatitis, gout, vasculitis, deep venous thrombosis, or a drug reaction, and one must be meticulous in identifying risk factors and performing a physical exam. Radiographic evaluation, such as an MRI, can aid in differentiating cellulitis from an underlying arthritis or osteomyelitis, and this is especially important in patients with diabetes, venous insufficiency, lymphedema, and recurrent symptoms. An abscess typically presents as a fluctuant mass that is painful, erythematous and often has surrounding inflammation.[26] Ultrasound is helpful in confirming an abscess when cellulitis features are also present. Other pathology that mimics an abscess includes epidermoid cysts, folliculitis, and hidradenitis suppurativa.

Treatment is based on the presence or absence of purulence. In cellulitis without purulence, empiric oral therapy should be initiated that covers beta-hemolytic streptococcus and methicillin-susceptible *Staphylococcus aureus* (MSSA) which includes cephalexin 500 mg QID or clindamycin 300–450 mg QID for those with severe beta-lactam allergies.[29] If systemic signs of toxicity (fever >100.4 °F, hypotension, sustained tachycardia), rapid progression of edema, persistence of symptoms beyond 48 h of oral antibiotic therapy, inability to tolerate oral therapy, or proximity of the lesion to an indwelling medical device, then intravenous therapy is recommended with cefazolin 1-2g TID. If there is concern for MRSA, then antibiotic regimens should include either oral agents such as trimethoprim-sulfamethoxazole 1-2 DS tablets BID, clindamycin 300–450 mg QID or intravenous agents such as vancomycin 20 mg/kg/dose BID or daptomycin 6 mg/kg daily. Improvement in symptoms should occur within 24–48 h, and alternative therapies or intravenous routes should be considered if none is witnessed. In most uncomplicated cases of cellulitis, 5 days of therapy is sufficient. Longer duration (up to 14 days) can be considered if there is a slower response to therapy or complicating factors such as immunosuppression.[27] In women with recurrent cellulitis infections, ≥4 episodes annually, alternative diagnoses must be entertained. Additionally, minimizing risk factors that precipitate cellulitis can be helpful, and daily suppressive therapy can be initiated which includes either penicillin V 250–500 mg BID or erythromycin 250 mg BID for beta-hemolytic streptococcal infections or clindamycin 150 mg daily or trimethoprim-sulfamethoxazole 1 DS tablet BID for staphylococcal infections. Blood cultures can aid in identifying pathogens, but cultures of intact skin do not yield helpful results in most cases.[30,31]

Purulent soft tissue infections with a drainable abscess should undergo incision and drainage. If the patient is at high risk for endocarditis, then antibiotic therapy that covers *S. aureus* and beta-hemolytic streptococcus should be administered 60 min prior to the procedure: trimethoprim-sulfamethoxazole, or clindamycin, or. Antibiotic treatment with clindamycin or trimethoprim-sulfamethoxazole should also follow if any of the following are present: single abscess ≥2 cm, multiple lesions, extensive cellulitis, immunosuppression, systemic toxicity, inadequate clinical response to incision and drainage alone, presence of an indwelling medical device, high risk for endocarditis, or high risk of transmission (athletes, military). However, recent studies have shown that initiation of clindamycin despite small lesions in uncomplicated patients yields higher cure rates and less recurrence.[32]

Purulent infections with no drainable abscess are most commonly harboring MRSA followed by MSSA and rarely beta-hemolytic streptococcus. Empiric therapy should be initiated to cover MRSA which includes clindamycin or trimethoprim-sulfamethoxazole, and this can be tailored based on culture results. Efficacy of these agents are similar, but there is an increased risk for *Clostridium difficile* with clindamycin use.[33]

The same indications apply to initiate intravenous therapy for an abscess as discussed for those with cellulitis; however, coverage for MRSA is necessary, and vancomycin or

daptomycin is recommended. Additionally, duration of therapy for purulent soft tissue infections, if needed, should be 5–14 days depending on clinical response and severity of symptoms which was also discussed previously for non-purulent infections.[26]

Infective endocarditis

In addition to soft tissue infections, infective endocarditis (IE) is a complication of IV opioid drug use. The incidence has been skewed by unreliable data, but 2–4 cases/1000 IV drug users is suspected.[34] When injecting opioids intravascularly, particulate matter often accompanies the drug and can cause endothelial damage to the tricuspid, aortic, and mitral valves in the heart.[35] Additionally, bacteria and fungus can contaminate the drug, syringe, or be found on the skin when injecting which can cause bacteremia and IE.[34] Chronic use may also cause cumulative damage to valves that predisposes for infection.[36] The most common pathogen found in over half of IE cases is *S. aureus* followed by streptococcus and enterococcus.[35]

There are important clinical findings in patients with IE suspected to be caused from IV drug use. Heart murmurs and systemic findings classical for IE might not be present which creates a challenge when evaluating an IV drug user with fever.[34] However, pneumonia, pulmonary septic emboli, and mycotic aneurysms of the pulmonary artery are a common finding that should prompt evaluation with echocardiogram. Additionally, positive blood cultures in patients who are IV drug users should prompt echocardiogram evaluation.[37] Heart failure is more common with aortic valve IE when compared to tricuspid valve IE. Metastatic infection that involves the brain, eye, spine, and kidneys is more commonly associated with IE in those that use IV drugs due to the spread of *S. aureus*.[38] Co-infections with HIV or hepatitis B and C can exacerbate clinical presentation and worsen outcomes.[34]

Treatment for IE ideally utilizes a prolonged course of parenteral antibiotics. Ideally, if a pregnant woman with OUD is hospitalized for a prolonged period of time to treat IE, attempts to transition to MAT and utilizing the hospitalization to take steps toward recovery should be made. However, IV drug users are typically non-compliant with remaining hospitalized for multiple weeks, and there is concern with allowing discharge of these patients with indwelling IV access to receive therapy at home or an infusion center due to the risk for abuse and injection of drugs through this portal. Therefore, shorter two-week parenteral courses and oral therapy has been suggested for uncomplicated IE from *S. aureus*. Contraindications for short-course or oral therapy for IE include involvement of the aortic or mitral valves, presence of highly resistant bacteria (methicillin-resistant *S. aureus*), or concurrent complications such as heart failure or valvular abscesses.[39] Prognosis of IE in IV drug users has not been shown to be impacted by HIV co-infection.[40] However, small reports show that mortality can be predicted in IV drug users with right-sided IE based on vegetation size. Vegetations <1 cm versus >1 cm revealed cure rates of 100 and 60%, respectively.[41] Additionally, heart failure was more likely in those with vegetations >1 cm.[42] Another study of more than 100 right-sided IE patients revealed mortality rates associated with vegetation sizes of <1, 1-2, >2 cm as 0, 3, 33%, respectively.[43]

Overdose

Perhaps the most significant morbidity associated with OUD and pregnancy is overdose. In the United States, drug overdose deaths quadrupled to 63,632 from 1999 to 2014, with 66.4% attributed to opioids.[44] Maternal death rates are also increasingly ascribed to overdose. In a cohort study of maternal death in Colorado, evaluation of opioid overdose and self-harm were pursued. Among the 211 total maternal deaths, 30% ($n = 63$) resulted from self-harm. The pregnancy-associated death ratio from overdose was 5.0 (95% confidence interval [CI] 3.4–7.2) per 100,000 live births and from suicide 4.6 (95% CI 3.0–6.6) per 100,000 live births. Detailed records were obtained for 94% ($n = 59$) of women with deaths from self-harm. Deaths were equally distributed throughout the first postpartum year (mean 6.21±3.3 months postpartum) with only six maternal deaths during pregnancy. Seventeen percent ($n = 10$) had a known substance use disorder. Prior psychiatric diagnoses were documented in 54% ($n = 32$) and prior suicide attempts in 10% ($n = 6$). Although half ($n = 27$) of the women with deaths from self-harm were noted to be taking psychopharmacotherapy at conception, 48% of them discontinued the medications during pregnancy. Fifty women had toxicology testing available; pharmaceutical opioids were the most common drug identified ($n = 21$).[45]

In a population-based retrospective cohort study, investigators utilized administrative and vital statistics databases in Massachusetts to estimate the rate of fatal and non-fatal overdoses among women with opioid use disorder who were treated with buprenorphine or methadone compared to those who were not.[46] The authors found an overall rate of overdose of 8.0 per 100,000 person-days. The highest overdose rate was at 7–12 months postpartum (12.3 per 100,000 person-days). Overall 64% of the 4,154 women with evidence of opioid use disorder received medication-assisted treatment in the year before delivery. Importantly, women who received buprenorphine or methadone had a lower rate of overdose in the early postpartum period (1.3 per 100,000 person-days versus 10.7 per 100,000 person-days from 4–6 months post-delivery) demonstrating the importance of MAT and ongoing provision of MAT after delivery.

Opioid overdose is more likely to occur in those that have use of additional sedatives, injection of illicit opioids of unknown potency and purity, co-occurring pulmonary disease, or sleep apnea. An area where pregnant PWID are at increased risk for overdose includes those with a recent abstinence from opiates such that the patient's tolerance to opioids is lowered. A dose that was previously tolerated may cause overdose in the abstinent patient. One can surmise that this mechanism could be contributing to maternal mortality statistics in the following scenario: pregnant PWID could try to abstain during pregnancy for the benefit of the baby or to avoid the influence of children's services, she then uses illicit drugs again immediately postpartum in the same doses as

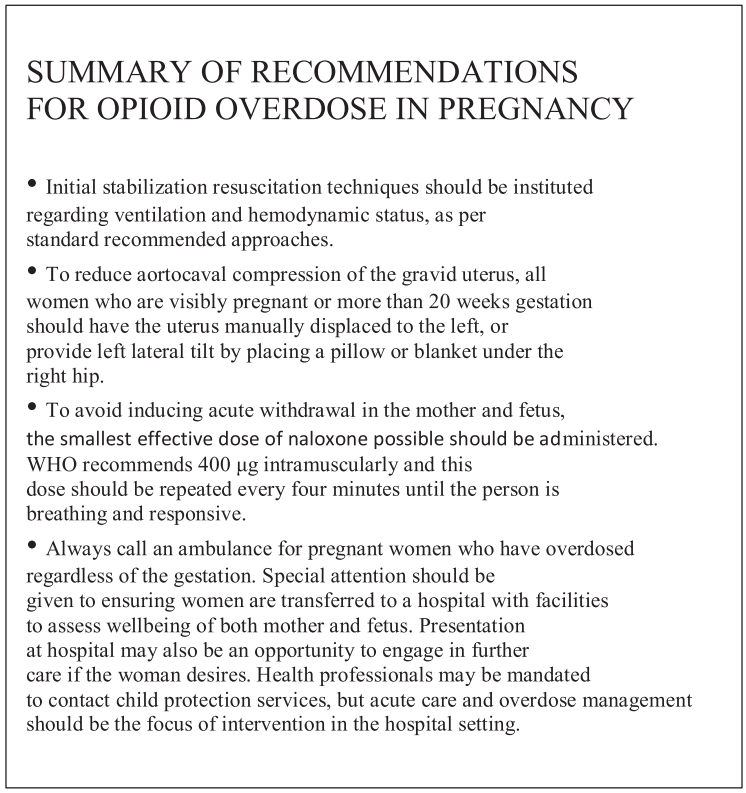

Fig. 1 – Summary of recommendations for opioid overdose in pregnancy.

prior to her period of abstinence, and she unintentionally overdoses.[47]

Programs of prescribing naloxone are integral to the care of pregnant women with OUD for overdose prevention. The unique management of using naloxone for management of overdose in pregnant PWID is outlined by Blandthorn et al. in Fig. 1, and highlights include minimizing aortocaval compression, maintaining the airway, utilizing naloxone in a dose of 400 μg when respiratory rate is 12 or less, and transport to a maternity hospital for continued monitoring. This allows for monitoring of maternal and fetal status, as well as provides the patient an opportunity to engage in treatment for OUD, should she desire.[48]

Conclusion

The associated medical complications of OUD in pregnancy are daunting, but one can be inspired by the many options that exist for primary prevention of complications. Rooted in harm-reduction: medication assisted treatment, vaccine programs, needle exchange programs, and naloxone prescribing represent tools for prevention of morbidity and mortality associated with OUD. In an ideal world, we will have effective strategies for primary prevention of OUD altogether. Until that time, we must work to ensure that clinicians capitalize on every opportunity for prevention of morbidity.

REFERENCES

1. Lugoboni F, Pajusco B, Albiero A, Quaglio G. Hepatitis A virus among drug users and the role of vaccination: a review. *Front Psychiatry*. 2011;2:79.
2. Hall HI, Song R, Rhodes P, et al. Estimation of HIV incidence in the United States. *JAMA*. 2008;300(5):520–529.
3. Prejean J, Song R, Hernandez A, et al. Estimated HIV incidence in the United States, 2006-2009. *PLoS One*. 2011;6(8):e17502.
4. Daniels D, Grytdal S, Wasley A, et al. Surveillance for acute viral hepatitis - United States, 2007. *MMWR Surveill Summ*. 2009;58(3):1–27.
5. Advisory Committee on Immunization, P. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-7):1–23.
6. www.cdc.gov/HAI/pdfs/bbp/exp-to-blood.pdf.
7. Magiorkinis G, Sypsa V, Magiorkinis S, et al. Integrating phylodynamics and epidemiology to estimate transmission diversity in viral epidemics. *PLoS Comput Biol*. 2013;9(1):e1002876.
8. Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson KE. Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. *Am J Public Health*. 1996;86(5):655–661.
9. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet*. 2011;378(9791):571–583.
10. ACOG committee opinion no. 752 summary: prenatal and perinatal human immunodeficiency virus testing. *Obstet Gynecol*. 2018;132(3):805–806.
11. ACOG committee opinion no. 751 summary: labor and delivery management of women with human immunodeficiency virus infection. *Obstet Gynecol*. 2018;132(3):803–804.

12. https://hab.hrsa.gov/livinghistory/issues/Women-And-Aids.pdf.
13. American College of Obstetrics and Gynecologists. ACOG practice bulletin no. 86: viral hepatitis in pregnancy. *Obstet Gynecol*. 2007;110(4):941–956.
14. Jourdain G, Ngo-Giang-Huong N, Harrison L. iTAP Study Group. Tenofovir to prevent perinatal transmission of hepatitis B. *N Engl J Med*. 2018;378(24):2350.
15. https://www.cdc.gov/hepatitis/hbv/perinatalxmtn.htm.
16. Society for Maternal-Fetal Medicine. Hepatitis C in pregnancy: screening, treatment, and management. *Am J Obstet Gynecol*. 2017;217(5):B2–B12.
17. Hepatitis C. AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. AASLD-IDSA HCV Guidance Panel. *Clin Infect Dis*. 2018;67(10):1477–1492. https://doi.org/10.1093/cid/ciy585.
18. Alavian SM, Mirahmadizadeh A, Javanbakht M, et al. Effectiveness of methadone maintenance treatment in prevention of hepatitis c virus transmission among injecting drug users. *Hepat Mon*. 2013;13(8):e12411.
19. Bruce RD. Methadone as HIV prevention: high volume methadone sites to decrease HIV incidence rates in resource limited settings. *Int J Drug Policy*. 2010;21(2):122–124.
20. Heimer R. Syringe exchange programs: lowering the transmission of syringe-borne diseases and beyond. *Public Health Rep*. 1998;113(Suppl 1):67–74.
21. Hwang LY, Grimes CZ, Tran TQ, et al. Accelerated hepatitis B vaccination schedule among drug users: a randomized controlled trial. *J Infect Dis*. 2010;202(10):1500–1509.
22. Ropponen A, Sund R, Riikonen S, Ylikorkala O, Aittomðki K. Intrahepatic cholestasis of pregnancy as an indicator of liver and biliary diseases: a population-based study. *Hepatology*. 2006;43(4):723–728.
23. Wijarnpreecha K, Thongprayoon C, Sanguankeo A, Upala S, Ungprasert P, Cheungpasitporn W. Hepatitis C infection and intrahepatic cholestasis of pregnancy: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol*. 2017;41(1):39–45.
24. Lindor KD and Lee RH. Intrahepatic Cholestasis of Pregnancy. UpToDate.com, accessed jan 2019.
25. McNamara DR, Tleyjeh IM, Berbari EF, et al. A predictive model of recurrent lower extremity cellulitis in a population-based cohort. *Arch Intern Med*. 2007;167(7):709–715.
26. Raff AB, Kroshinsky D. Cellulitis: a review. *JAMA*. 2016;316(3):325–337.
27. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis*. 2014;59(2):147–159.
28. Summanen PH, Talan DA, Strong C, et al. Bacteriology of skin and soft-tissue infections: comparison of infections in intravenous drug users and individuals with no history of intravenous drug use. *Clin Infect Dis*. 1995;20(Suppl 2):S279–S282.
29. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52(3):285–292.
30. Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med*. 2013;368(18):1695–1703.
31. Klempner MS, Styrt B. Prevention of recurrent staphylococcal skin infections with low-dose oral clindamycin therapy. *JAMA*. 1988;260(18):2682–2685.
32. Daum RS, Miller LG, Immergluck L, et al. A placebo-controlled trial of antibiotics for smaller skin abscesses. *N Engl J Med*. 2017;376(26):2545–2555.
33. Bowen AC, Lilliebridge RA, Tong SY, et al. Is Streptococcus pyogenes resistant or susceptible to trimethoprim-sulfamethoxazole? *J Clin Microbiol*. 2012;50(12):4067–4072.
34. Sande MA, Lee BL, Mills J, et al. *Endocarditis in intravenous drug users*. *Infect Endocarditis*; 1992345.
35. Mathew J, Addai T, Anand A, Morrobel A, Maheshwari P, Freels S. Clinical features, site of involvement, bacteriologic findings, and outcome of infective endocarditis in intravenous drug users. *Arch Intern Med*. 1995;155(15):1641–1648.
35. Pons-Lladœ G, Carreras F, BorrÃs X, et al. Findings on Doppler echocardiography in asymptomatic intravenous heroin users. *Am J Cardiol*. 1992;69(3):238–241.
37. Mller KA, Zrn CS, Patrik H, et al. Massive haemoptysis in an intravenous drug user with infective tricuspid valve endocarditis. *BMJ Case Rep*. 2010;2010.
38. Ruotsalainen E, Sammalkorpi K, Laine J, et al. Clinical manifestations and outcome in Staphylococcus aureus endocarditis among injection drug users and nonaddicts: a prospective study of 74 patients. *BMC Infect Dis*. 2006;6:137.
39. Torres-Tortosa M, de Cueto M, Vergara A, et al. Prospective evaluation of a two-week course of intravenous antibiotics in intravenous drug addicts with infective endocarditis. Grupo de Estudio de Enfermedades Infecciosas de la Provincia de Cadiz. *Eur J Clin Microbiol Infect Dis*. 1994;13(7):559–564.
40. Ribera E, Mirœ JM, CortÕs E, et al. Influence of human immunodeficiency virus 1 infection and degree of immunosuppression in the clinical characteristics and outcome of infective endocarditis in intravenous drug users. *Arch Intern Med*. 1998;158(18):2043–2050.
41. Robbins MJ, Frater RW, Soeiro R, Frishman WH, Strom JA. Influence of vegetation size on clinical outcome of right-sided infective endocarditis. *Am J Med*. 1986;80(2):165–171.
42. Bayer AS, Blomquist IK, Bello E, Chiu CY, Ward JI, Ginzton LE. Tricuspid valve endocarditis due to Staphylococcus aureus. Correlation of two-dimensional echocardiography with clinical outcome. *Chest*. 1988;93(2):247–253.
43. Hecht SR, Berger M. Right-sided endocarditis in intravenous drug users. Prognostic features in 102 episodes. *Ann Intern Med*. 1992;117(7):560–566.
44. Hedegaard H, Warner M, Minino AM. Drug overdose deaths in the United States, 1999-2016. *NCHS Data Brief*. 2017(294):1–8.
45. Metz TD, Rovner P, Hoffman MC, Allshouse AA, Beckwith KM, Binswanger IA. Maternal deaths from suicide and overdose in Colorado, 2004-2012. *Obstet Gynecol*. 2016;128(6):1233–1240.
46. Schiff DM, Nielsen T, Terplan M, et al. Fatal and nonfatal overdose among pregnant and postpartum women in Massachusetts. *Obstet Gynecol*. 2018;132(2):466–474.
47. Darke S, Hall W. Heroin overdose: research and evidence-based intervention. *J Urban Health*. 2003;80(2):189–200.
48. Blandthorn J, Bowman E, Leung L, Bonomo Y, Dietze P. Managing opioid overdose in pregnancy with take-home naloxone. *Aust N Z J Obstet Gynaecol*. 2018;58(4):460–462.