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THE TREATMENT OF ALCOHOL AND OPIOID DEPENDENCE IN PREGNANT WOMEN

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Abstract

Purpose of the review—This article addresses the question of "best treatment options," which clinicians face when treating pregnant women with alcohol and/or opioid dependence.

Recent findings

Alcohol: Studies show that alcohol consumption is associated with fetal abnormalities and long-term cognitive problems depending on amount consumed, drinking pattern, and time of gestation. Screening and evaluation of specific interventions are important to reduce alcohol consumption during pregnancy and associated problems in infants.

Opioids: Withdrawal-induced fetal distress and the risk of relapse are the primary reasons why opioid detoxification is only recommended in the second or third trimesters and only in those pregnant women who refuse opioid maintenance therapy (OMT). Methadone is the most established treatment of pregnant opioid-dependent women, but recent investigations suggest that substitution with buprenorphine may have advantages over methadone in terms of neonatal abstinence syndrome (NAS). Promising results have been also reported for slow-release oral methadone and the heroin equivalent diamorphin.

Summary—Data regarding the pharmacological treatment of alcohol abuse and/or dependence is limited in pregnant women. So far, benzodiazepines seem to be the most recommendable option for managing alcohol withdrawal, and psychosocial interventions succeed in reducing alcohol consumption or in maintaining abstinence in alcohol-dependent pregnant women. Recent data, albeit preliminary, support the use of naltrexone in the treatment of alcohol-dependent pregnant women.

Regarding opioid dependence meta-analyses do not clearly support the superiority of one substitute over the other during pregnancy owing to the presence of interfering factors (such as illicit drug use) in the studies conducted. Current results suggest that factors like the health status

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of the mother, the need for additional medications (e.g. treatment for HIV), comorbid drug dependence, and concurrent drug use need to be considered in order to find the “best opioid substitute”. Further considerations include the expectant mother’s compliance level to the treatment and the degree to which she tolerates the respective substitute.

Keywords

Opiates; Opioid dependence; alcohol dependence; pregnancy; medication; opioid maintenance treatment; childbearing

I. Introduction

It is estimated that 47 percent of pregnant women abuse alcohol and 6 percent use illegal drugs [1]. The European Monitor Centre for Drugs and Drug Addiction reports that about half a million of opioid-dependent Europeans are in opioid maintenance therapy (OMT) [2] and that in Europe, around 30.000 opioid-dependent women get pregnant [3]. Although, moderate alcohol consummation during pregnancy has not been associated with deleterious fetal effects [4], alcohol and/or opioid use disorders during pregnancy carries several risks such as fetal alcohol syndrome (FAS), spontaneous abortion, intrauterine growth restriction, antepartum hemorrhage, preterm delivery, and stillbirth [5]. Proven treatment options regarding alcohol and opioid dependence are limited owing to the complexity of substance dependence and the lack of data from randomized controlled trials (RCTs).

In summary, there is a crucial need to improve treatments for alcohol and opioid dependence in pregnant women and this review will focus specifically on the current research regarding the risks and the benefits of certain treatment options for alcohol- and/or opioid-dependent pregnant women. The review addresses the risks of alcohol or opioid withdrawal in pregnant patients and summarizes the few available data regarding the clinical implementation of OMT and pharmacological treatments for alcoholism in pregnant women.

The studies discussed here were found using several keywords on MEDLINE and PubMed (e.g. “alcohol”, “methadone,” “buprenorphine,” “opiates,”, “opioids”, “diamorphine”, “slow release oral morphine”, “pregnancy,” “cognitive development”, “development”) as well as by searching the bibliographies of relevant papers.

II. INTRAUTERINE EXPOSURE TO ALCOHOL/OPIOIDS

II (a) Alcohol

Alcohol consumption during pregnancy—It is well established that alcohol consumption during pregnancy is associated with fetal malformations (particularly alcohol-induced fetopathy) and long-term psychological problems in the offspring [6–10]. Nevertheless, population-based studies show a high frequency of alcohol consumption in pregnant women. For example, a large Norwegian study documented a rate of 25% of binge drinking during the first six weeks of pregnancy, before the mother was aware of the pregnancy. After the mother became aware of the pregnancy, binge drinking in the study population dropped below 2% and general alcohol consumption from 89 % pre-pregnancy to 23% after 12 weeks [11]. The association between specific amounts of alcohol consumed

and developmental problems is still an area under investigation. A recently published systematic review shows evidence for a dose-related risk for preterm birth, small gestational age, and low birthweight with heavy alcohol consumption but not with low to moderate consumption [12]. Similar results were described earlier by Henderson and colleagues, who showed no significant effects on pregnancy outcome parameters for low or moderate alcohol consumption [13]. A recent analysis of different previous investigations reports that alcohol consumption of more than four drinks a day is associated with negative effects on motor function in the child [14]. However, data regarding the effects of low or moderate alcohol consumption on pregnancy outcome parameters is still inconclusive. Therefore, the absence of a significant association cannot imply that low or moderate alcohol consumption is generally safe, particularly because little is known on the long-term effects in the child [15]. Finally, the drinking pattern (e.g. binge drinking) and the gestational age of the exposed fetus both seem to additionally increase the risk of mental problems in the child [16, 17].

Diagnosis of problematic alcohol consumption in pregnant women—Alcohol consumption can be evaluated using psychometric tools as well as biomarkers. Psychometric screening for alcohol consumption in pregnant women uses the same tools as in other populations. In addition, more specific assessment instruments are available, such as TWEAK (five questions) and T-ACE (four questions) [18–21] (see also Table 1).

The Alcohol Use Disorder Identification Test (AUDIT) has also shown good predictive properties in the assessment of elevated-risk drinking in pregnant women [22, 23], while other instruments like CAGE and the Michigan Alcohol Screening Test (MAST) were less effective in some studies [24, 25]. The data yielded by using these instruments suggests that combining psychometric testing with biomarkers such as liver enzymes, mean corpuscular volume, ethyl glucuronide, and ethyl sulfate facilitates the diagnosis of excessive alcohol consumption in pregnant patients [26, 27]. In contrast, carbohydrate-deficient transferrin (CDT) seems to be less valuable as a diagnostic tool as its blood levels are independently associated with the gestational week and increase during pregnancy [28].

II (b) Opioids

Opioid exposure in utero—There is little data concerning the neurobiological effects of opioid exposure in utero and it is unclear whether prolonged opioid exposure may have detrimental effects on developing nerve cells. Endogenous opioids do participate in controlling cellular proliferation [29], and even therapeutic dosages of buprenorphine have been found to disrupt the myelinisation of nerve cells [30, 31]. Moreover, opioids stimulate the release of dopamine, which affects neurite outgrowth and branching [32].

Opioid intake during pregnancy has been associated with negative effects on the fetus exposed in utero. For example, volumetric research consistently shows a decrease of prenatal head growth [33] and brain volume [34] even in children of opioid maintained women. Although there is insufficient clinical data regarding the reduction of brain volume by the standard substitute medications buprenorphine and methadone, preclinical data suggests that OMT may be similar to heroin consumption in its effects on brain volume [35, 36]. Moreover, OMT is thought to be associated with cognitive impairment in areas such as

reading abilities, visuospatial working memory, problem solving skills and recognition memory [31]. This hypothesis is supported by results from preclinical studies that point towards alterations not only in dopaminergic but also in catecholaminergic [37] neurotransmission caused by opioid exposure in utero. Studies controlled for environmental factors (including social deprivation and affection of the parent-child-interaction due to neonatal withdrawal symptoms [38]) link opioid exposure in utero with worse performance in intelligence testing and with high incidences of psychiatric disease [5].

III. THE TREATMENT OF ALCOHOL/OPIOID-DEPENDENT PREGNANT WOMEN

III (a) Treatment of alcohol dependence in pregnant women

Because of the severe consequences of sustained heavy alcohol consumption during pregnancy, treatment of alcohol dependence and alcohol abuse in pregnant women is a very important clinical need. Usually, abstinence after previous detoxification in an inpatient setting can be considered as first-choice in the treatment of alcohol dependent patients or women with high alcohol consumption. However, in individual cases, when total abstinence is an unrealistic therapeutic goal, a reduction in the amount of alcohol consumption and number of heavy drinking days may also be considered a possible treatment goal [39, 40]. In either case, a close collaboration with an obstetrician is of high importance to monitor the risk to the fetus.

ALCOHOL DETOXIFICATION—Pregnant patients must be advised against stopping drinking “cold turkey”. During inpatient detoxification the use of pharmacological therapy should be considered even earlier than in patients who are not pregnant since withdrawal and the associated elevated stress levels may represent a much higher risk to the fetus than the use of safe pharmacological agents [41, 42].

Benzodiazepines can be considered a first-line pharmacological treatment for patients who are not pregnant [43–45]. No data from clinical studies is available, however, regarding the use of benzodiazepines for treating alcohol withdrawal during pregnancy. There is some evidence suggesting negative effects particularly during the first trimester as well as during the last weeks of pregnancy. In fact, benzodiazepine use in the first trimester has been associated with an elevated risk of oral clefts and other malformations [46], but these results are controversial [47–49]. In addition, the use of benzodiazepines in the last weeks of pregnancy carries the risk of postnatal withdrawal syndrome as well as perinatal problems like floppy-infant syndrome [50]. These potential risk factors have to be taken into account, although they can be well managed in the majority of patients [43, 44].

Clomethiazole, which is widely used in Central Europe [51], should not be used in pregnant women because the risk of possible teratogenic effects cannot be ruled out. Other medications used in treating alcohol withdrawal symptoms, such as anticonvulsants, are also associated with a higher risk of fetal malformations and should only be prescribed after a careful consideration of the effects of withdrawal against the possible implications of the pharmacological treatment [52, 53].

REDUCTION OF ALCOHOL CONSUMPTION AND PREVENTION OF ALCOHOL RELAPSE—Psychosocial interventions may help to reduce alcohol consumption or strengthen abstinence in pregnant patients. Brief interventions aimed at reducing alcohol consumption have shown promising results in pregnant women [54–56], while research has shown that the effect of screening on drinking is undervalued [57]. A recent Cochrane database review has highlighted that there is still limited evidence regarding the effectiveness of different psychological or educational interventions [58].

In the last decades, pharmacotherapies for alcohol dependence have gained a great amount of attention, i.e. disulfiram [59], naltrexone (tablets and intramuscular) [Garbutt, 2010], acamprosate [60], topiramate [61], baclofen [62] and ondansetron [63].

A recent study showed that there is strong interest in pharmacological treatment to reduce drinking among pregnant patients [64]. However, the data on teratogenic or toxic effects of these compounds during pregnancy is very limited. Hence no definitive recommendations can be given concerning these medications during pregnancy, and they should only be administered on a case-by-case basis and after careful evaluation. For example, according to the Food and Drug Administration (FDA) classification, ondansetron is in the pregnancy category B, while disulfiram, naltrexone, acamprosate and baclofen are in the pregnancy category C. Topiramate was recently reclassified from category C to category D, based on new data reporting an increased risk for cleft lip and/or cleft palate (oral clefts). On the other hand, naltrexone shows potential for use in pregnant alcohol-dependent women. For example, in a recent animal study, a naltrexone-implant formulation was well tolerated in pregnant rats [65]. Other studies suggest good tolerability of naltrexone during pregnancy in opioid-dependent patients [66, 67]. In summary, some data, albeit preliminary, suggest that naltrexone may be considered as a treatment option when treating pregnant alcohol-dependent patients, although additional studies are needed.

III (b) Treatment of opioid dependence in pregnant women

OPIOID DETEXOFICATION—Most studies report no increase in obstetrical complications due to opioid withdrawal in the second and third trimester [68]. Nevertheless, after weighing the potential risks of withdrawal-induced fetal distress and the possible changes in epigenetic programming it may cause [69] as well as the high risk of relapse in opioid-dependent women, it is possible to conclude that opioid detoxification therapy is only recommended for pregnant women who refuse OMT [70]. OMT is known to increase patient's health status in general and to reduce the harmful effects of illegal drug use (such as cocaine and amphetamines). For that reason, OMT is the actual standard of care for pregnant opioid-dependent women [71].

OPIOID MAINTAINANCE THERAPY (OMT)—Studies suggest that both methadone and buprenorphine are safe for OMT in pregnant women [72–74]. Some differences were found, however, on fetal head growth, suggesting that fetuses exposed to methadone may be at higher risk for stunted head growth as compared to those exposed to buprenorphine. However, these studies were not controlled for potential bias such as concurrent drug or nicotine use or social differences, which may reduce the generalizability of the results [5, 73,

75]. The main reason for preferring buprenorphine over methadone is the relatively mild neonatal withdrawal syndrome (NWS) in neonates exposed to buprenorphine in utero [76–78]. However, since opioid withdrawal symptoms need to manifest before buprenorphine is administered, the advantage of milder NWS as compared with methadone replacement therapy is washed out. In addition, many patients refuse buprenorphine treatment for that reason. OMT using buprenorphine is therefore only indicated for maintainance of an existing buprenorphine treatment or when heroin-using patients are treated. The data available to date does not support a shift from methadone to buprenorphine if patients get pregnant [76–78].

There are only case studies regarding slow-release oral morphine (SROM) and diamorphin (DAM), which indicate that both substances may be safe during pregnancy [79]. Although the results are sparse, some studies report less concurrent drug use (e.g. benzodiazepines and opioids) by pregnant women treated with SROM as compared to women on methadone maintainance [79]. Only a few case studies have been published on the use of DAM in pregnant women and might suggest a good tolerance and a relatively mild NWS [80, 81].

IV. Conclusion

Alcohol

Heavy alcohol consumption is associated with fetal malformations, pregnancy complications and long-term developmental disorders in children. As a first step, screening pregnant women with a combined assessment of psychometric tests and biomarkers helps to evaluate the individual risks. Identification of problematic alcohol consumption allows the subsequent use of brief interventions to reduce problematic consumption patterns. In the case of alcohol dependence, detoxification with benzodiazepines, combined with intensive psychosocial support, should be the treatment of first choice. The use of pharmaceutical agents cannot be recommended for relapse prevention in pregnant women because of the limited knowledge of possible toxic or teratogenic effects.

Opioids

Opioid maintenance therapy (OMT) is the standard of care in opioid-dependent patients, reasoned by their high risk of relapse. Both methadone and buprenorphine seem safe treatment strategies in opioid-dependent pregnant women. Further data indicates the safety of DAM and SROM as well. Limited data supports advantages of DAM, SROM and buprenorphine against methadone regarding NWS and concurrent drug use.

Overall, the mother’s health status and her acceptance of the recommended substitute should be the foundation of a personalized therapeutic regimen of OMT in pregnant women.

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Table 1

T-ACE and TWEAK screening questionnaires.

T-ACE*	**TWEAK****
T. Tolerance: How many drinks does it take to make you feel high? **A.** Have people **Annoyed** you by criticizing your drinking? **C.** Have you ever felt you ought to **Cut down** on your drinking? **E. Eye Opener:** Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? **T-ACE scoring system**: 2 points for a positive response to question T (> 2 drinks); 1 point each for a positive response to question A, C or E. A total score of ≥2 indicates a positive outcome for pregnancy risk drinking.	**T. Tolerance:** How many drinks can you hold? **W.** Have close friends or relatives **Worried** or complained about your drinking in the past year? **E. Eye Opener:** Do you sometimes take a drink in the morning when you get up? **A Amnesia:** Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember? **K(C).** Do you sometimes feel the need to **Cut down** on your drinking? **TWEAK scoring system**: 2 points each for a positive response to question T (> 5 drinks) or W; 1 point each for a positive response to question E, A, or K. A total score of ≥ 2 indicates a positive outcome for pregnancy risk drinking.

Sources:

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Sokol et al. 1989 [16];

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Chan et al. 1993 [17].